Connecting via Winsock to STN

* * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:57:19 ON 14 SEP 2006

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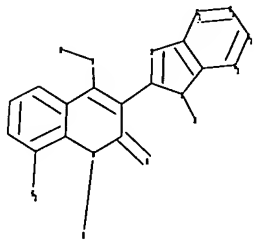
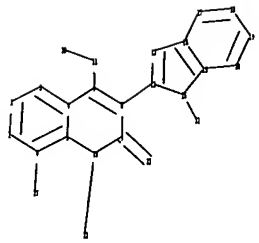
Uploading C:\Program Files\Stnexp\Queries\10644055.str





chain nodes :
11 21 22 23 27 28
ring nodes :
1 2 3 4 5 6 7 8 9 10 12 13 14 15 16 17 18 19 20
chain bonds :
6-27 7-11 8-12 9-23 10-22 11-28 16-21
ring bonds :
1-2 1-6 2-3 3-4 4-5 4-7 5-6 5-10 7-8 8-9 9-10 12-13 12-16 13-14 14-15
14-17 15-16 15-20 17-18 18-19 19-20
exact/norm bonds :

4-7 5-10 6-27 7-8 7-11 8-9 8-12 9-10 9-23 10-22 11-28 12-13 12-16
13-14 14-15 14-17 15-16 15-20 16-21 17-18 18-19 19-20
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6
isolated ring systems :
containing 1 : 12 :

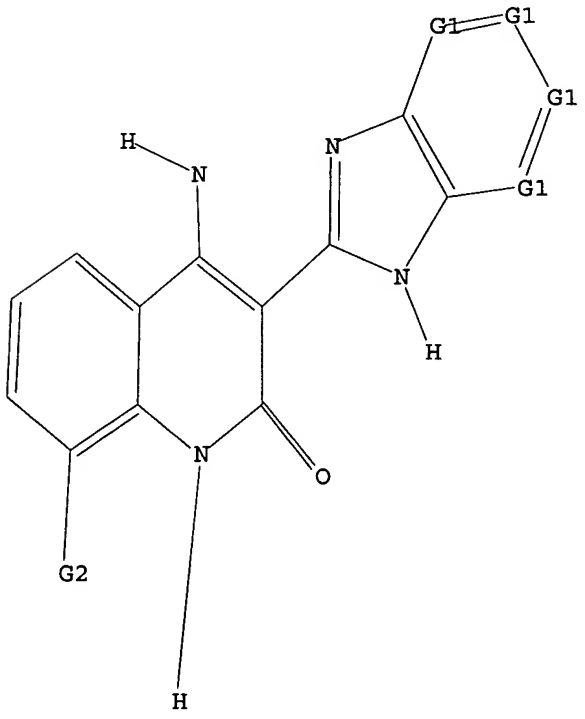
G1:C,N

G2:H,Ak

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:CLASS 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom 21:CLASS 22:CLASS 23:CLASS 27:CLASS 28:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR




G1 C,N
G2 H,Ak

Structure attributes must be viewed using STN Express query preparation.

=> s l1 full

```
L3          1572 SEA SSS FUL L1

=> file ca


=> s l3
L4            19 L3

=> s tyrosine kinase
         150162 TYROSINE
         265955 KINASE
L5        36780 TYROSINE KINASE
                (TYROSINE(W)KINASE)

=> s l4 and l5
L6            12 L4 AND L5

=> d ibib abs fhitstr 1-12
```

L6 ANSWER 1 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 145:202872 CA
TITLE: Treatment of metastasized tumors
INVENTOR(S): Lopes De Menezes, Daniel; Heise, Carla; Xin, Xiaohua
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 101pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

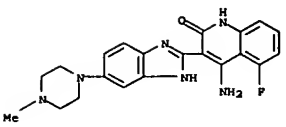
| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2006081445 | A2 | 20060803 | WO 2006-US2979 | | 20060127 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| US 2006183750 | A1 | 20060817 | US 2006-342257 | | 20060127 |
| PRIORITY APPLN. INFO.: | | | US 2005-647568P | P | 20050127 |
| | | | US 2005-669245P | P | 20050406 |
| | | | US 2005-722053P | P | 20050929 |

AB Methods of treating metastatic cancer such as metastasized tumors include administering a compound of Structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable salt or the tautomer, or a mixture thereof to a subject. The compound, tautomer, salt of the compound, salt of the tautomer, or mixture thereof may be used to prepare medicaments for treating metastatic cancer. The variable A has the values defined herein.

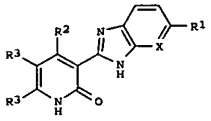
IT 405169-16-6P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(treatment of metastasized tumors)

RN 405169-16-6 CA
CN 2(1H)-Quinolinone, 4-amino-5-fluoro-3-[5-(4-methyl-1-piperazinyl)-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)

L6 ANSWER 1 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)



L6 ANSWER 2 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 144:450655 CA
TITLE: Design and structure-activity relationship of heterocyclic analogs of 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones as inhibitors of receptor tyrosine kinases
AUTHOR(S): Frazier, Kelly; Jazan, Elisa; McBride, Christopher M.; Pecchi, Sabina; Renhowe, Paul A.; Shafer, Cynthia M.; Taylor, Clarke; Bussiere, Dirksen; He, Molly Min; Jansen, Johanna M.; Lapointe, Gena; Ma, Sylvia; Vora, Jayesh; Wiesmann, Marion
CORPORATE SOURCE: Small Molecule Drug Discovery, Biopharma Division, Chiron Corporation, Emeryville, CA, 94608, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(8), 2247-2251
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:450655
GI



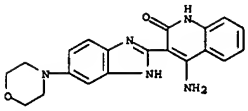
I

AB A series of novel heterocyclic analogs of the 4-amino-3-benzimidazol-2-yl quinolin-2-one, heterocycle-fused (aza)benzimidazolyl pyridinones I (X = CH, N; R1 = H, 4-morpholinyl, 4-methyl-1-piperazinyl; R2 = HO, H2N; R3C:CR3 = benzene, pyridine, thiophene, imidazole, pyrazole), is described. These compds. are potent inhibitors of receptor tyrosine kinases and exhibit favorable pharmacokinetic profiles. The synthesis and SAR of these compds. are described.

IT 405168-36-7P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and structure-activity relationship of heterocyclic analogs of amino(benzimidazolyl)quinolinone as inhibitors of receptor tyrosine kinases)

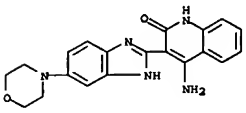
RN 405168-36-7 CA
CN 2(1H)-Quinolinone, 4-amino-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)

L6 ANSWER 2 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 144:232902 CA
TITLE: LHMDS mediated tandem acylation-cyclization of 2-aminobenzenecarbonitriles with 2-benzimidazol-2-yl acetates: a short and efficient route to the synthesis of 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones
AUTHOR(S): Antonios-McCrea, William R.; Frazier, Kelly A.; Jazan, Elisa M.; Machajewski, Timothy D.; McBride, Christopher M.; Pecchi, Sabina; Renhowe, Paul A.; Shafer, Cynthia M.; Taylor, Clarke
CORPORATE SOURCE: Small Molecule Drug Discovery, Medicinal Chemistry Department, Chiron Corporation, Emeryville, CA, 94608, USA
SOURCE: Tetrahedron Letters (2006), 47(5), 657-660
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The discovery of a mild, one-pot tandem acylation-cyclization for the synthesis of 4-amino-3-(2-benzimidazolyl)quinolinone derivs. from 2-aminobenzonitrile derivs. and Et (2-benzimidazolyl)acetate derivs. is described. Among the reagents evaluated, lithium hexamethyldisilazide (LHMDS) was the most efficient.
IT 405168-36-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (amino)(benzimidazolyl)quinolinone derivs. via lithium hexamethyldisilazide-mediated tandem acylation-cyclization reaction using benzimidazole-2-acetic acid ester and (amino)benzonitrile as reactants)
RN 405168-36-7 CA
CN 2(1H)-Quinolinone, 4-amino-3-[5-(4-morpholinyl)-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)



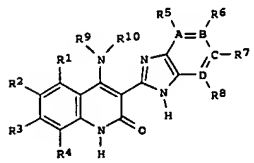
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:477969 CA
TITLE: Preparation of benzimidazole quinolinones for inhibiting FGFR3 and treating multiple myeloma
INVENTOR(S): Cai, Shaopei; Chou, Joyce; Harwood, Eric; Heise, Carla C.; Machajewski, Timothy D.; Ryckman, David; Shang, Xiao; Wiesmann, Marion; Zhu, Shuguang
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 239 pp., Cont.-in-part of U.S. Ser. No. 644,055.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2005261307 | A1 | 20051124 | US 2004-983174 | | 20041105 |
| US 2004092535 | A1 | 20040513 | US 2003-644055 | | 20030819 |
| CN 1692112 | A | 20051102 | CN 2003-824565 | | 20030819 |
| US 2005203101 | A1 | 20050915 | US 2004-839793 | | 20040505 |
| PRIORITY APPLN. INFO.: | | | US 2002-405729P | P | 20020823 |
| | | | US 2002-426107P | P | 20021113 |
| | | | US 2002-426226P | P | 20021113 |
| | | | US 2002-426282P | P | 20021113 |
| | | | US 2002-428210P | P | 20021121 |
| | | | US 2003-460327P | P | 20030403 |
| | | | US 2003-460328P | P | 20030403 |
| | | | US 2003-460493P | P | 20030403 |
| | | | US 2003-478916P | P | 20030616 |
| | | | US 2003-484048P | P | 20030701 |
| | | | US 2003-644055 | A2 | 20030819 |
| | | | US 2003-517915P | P | 20031107 |
| | | | US 2003-526425P | P | 20031202 |
| | | | US 2003-526426P | P | 20031202 |
| | | | US 2004-546017P | P | 20040219 |

OTHER SOURCE(S): MARPAT 143:477969
GI

L6 ANSWER 4 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)



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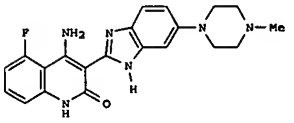
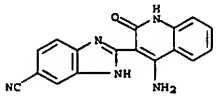


II

AB The title compds. I [A, B, C, and D = C, N; R1-R3 = H, halo, CN, NO2, etc.; R4 = H, alkyl; R5-R8 = H, halo, CN, NO2, etc.; R9 = H, (un)substituted alkyl, aryl, etc.; R10 = H], useful for inhibiting fibroblast growth factor receptor 3 or treating a biol. condition mediated by fibroblast growth factor receptor 3, were prepared E.g., a multi-step synthesis of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one (II), starting from 5-chloro-2-nitroaniline and 1-methylpiperazine, was given. The majority of the exemplary compds. I displayed an IC50 of less than 10 μM with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1α, Raf, Fyn, Lck, Rsk2, PAR-1, c-Kit, c-ABL, p60src, FGFR3, FLT-3, PDGFRα, and PDGFRβ. In addition, many of the exemplary compds. exhibited IC50 values in the nM range and show potent activity with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR3, c-Kit, c-ABL, FLT-3, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, MEK1, CHK2, Fyn, Lck, Rsk2, PAR-1, PDGFRα, and PDGFRβ with IC50 values of less than 1 μM. The mentioned above compound II was tested in various tests and showed significant antiproliferative activity. II inhibited FGFR3 receptor phosphorylation and ERK phosphorylation in multiple myeloma cell lines with activating FGFR3 mutations.
IT 405168-20-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of benzimidazole quinolinones for inhibiting FGFR3 and treating multiple myeloma)
RN 405168-20-9 CA

L6 ANSWER 4 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)
CN 1H-Benzimidazole-5-carbonitrile, 2-(4-amino-1,2-dihydro-2-oxo-3-quinolinyl)- (9CI) (CA INDEX NAME)



L6 ANSWER 5 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:279443 CA
TITLE: 4-Amino-3-(benzimidazol-2-yl)quinolin-2-one derivatives for the modulation of inflammatory and metastatic processes
INVENTOR(S): Lee, Sang H.; Heise, Carla C.
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2005082340 | A2 | 20050909 | WO 2005-US5316 | | 20050218 |
| WO 2005082340 | A3 | 20060504 | | | |
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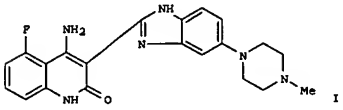
| US 2005239825 | A1 | 20051027 | US 2005-61386 | | 20050218 |
| PRIORITY APPLN. INFO.: | | | US 2004-546395P | P | 20040220 |
| | | | US 2004-547103P | P | 20040223 |
| | | | US 2004-554771P | P | 20040319 |

OTHER SOURCE(S): MARPAT 143:279443
GI

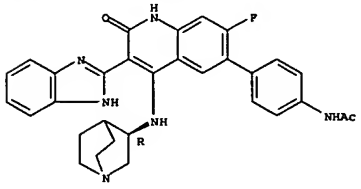


I

AB The invention provides methods for using of using 4-Amino-3-(benzimidazol-2-yl)quinolin-2-one derivs. (Markush included), or a salt or tautomer thereof, in the treatment of disorders relating to cell adhesion and metastatic processes. Preparation of I is included.

L6 ANSWER 5 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)
IT 668481-36-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bOenzimidazolyl aminoquinolinone derivs. for modulation of inflammatory and metastatic processes)
RN 668481-36-5 CA
CN Acetamide, N-[4-[4-[(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-7-fluoro-1,2-dihydro-2-oxo-6-quinolinyl]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 6 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:7710 CA
TITLE: Preparation of benzimidazole quinolinones for inhibiting FGFR3 and treating multiple myeloma
INVENTOR(S): Cai, Shaopei; Chou, Joyce; Harwood, Eric; Heise, Carla C.; Machajewski, Timothy D.; Ryckman, David; Shang, Xiao; Wiesmann, Marion; Zhu, Shuguang
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 567 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2005047244 | A2 | 20050526 | WO 2004-US36956 | | 20041105 |
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| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
| AU 2004289672 | A1 | 20050526 | AU 2004-289672 | | 20041105 |
| CA 2544186 | AA | 20050526 | CA 2004-2544186 | | 20041105 |
| US 2005137399 | A1 | 20050623 | US 2004-982757 | | 20041105 |
| US 2005209247 | A1 | 20050922 | US 2004-982543 | | 20041105 |
| EP 1692085 | A2 | 20060823 | EP 2004-810419 | | 20041105 |
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| PRIORITY APPLN. INFO.: | | | US 2003-517915P | P | 20031107 |
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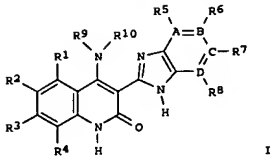
| | | | US 2004-546017P | P | 20040219 |
| | | | WO 2004-US36956 | W | 20041105 |

OTHER SOURCE(S): MARPAT 143:7710
GI



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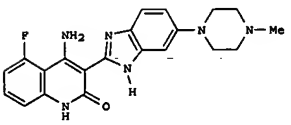
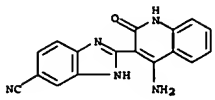


II

AB The title compds. I [A, B, C, and D = C, N; R1-R3 = H, halo, CN, NO2, etc.; R4 = H, alkyl; R5-R8 = H, halo, CN, NO2, etc.; R9 = H, (un)substituted alkyl, aryl, etc.; R10 = H], useful for inhibiting fibroblast growth factor receptor 3 or treating a biol. condition mediated by fibroblast growth factor receptor 3, were prepared E.g., a multi-step synthesis of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one (II), starting from 5-chloro-2-nitroaniline and 1-methylpiperazine, was given. The majority of the exemplary compds. I displayed an IC50 of less than 10 μM with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1α, Raf, Fyn, Lck, Rsk2, PAR-1, c-Kit, c-ABL, p60src, FGFR3, FLT-3, PDGFRα, and PDGFRβ. In addition, many of the exemplary compds. exhibited IC50 values in the nM range and show potent activity with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR3, c-Kit, c-ABL, FLT-3, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, MEK1, CHK2, Fyn, Lck, Rsk2, PAR-1, PDGFRα, and PDGFRβ with IC50 values of less than 1 μM. The mentioned above compound II was tested in various tests and showed significant antiproliferative activity. II inhibits FGFR3 receptor phosphorylation and ERK phosphorylation in multiple myeloma cell lines with activating FGFR3 mutations.

IT 405168-20-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of benzimidazole quinolinones for inhibiting FGFR3 and treating multiple myeloma)
RN 405168-20-9 CA
CN 1H-Benzimidazole-5-carbonitrile, 2-(4-amino-1,2-dihydro-2-oxo-3-

L6 ANSWER 6 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)
quinolinyl)- (9CI) (CA INDEX NAME)



L6 ANSWER 7 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:7709 CA
TITLE: Preparation of benzimidazole quinolinones and lactate salts thereof for inhibiting vascular endothelial growth factor receptor tyrosine kinase
INVENTOR(S): Cai, Shaopei; Chou, Joyce; Harwood, Eric; Machajewski, Timothy D.; Ryckman, David; Shang, Xiao; Zhu, Shuguang
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 215 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005046589 | A2 | 20050526 | WO 2004-US36941 | 20041105 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2004288692 | A1 | 20050526 | AU 2004-288692 | 20041105 |
| CA 2544492 | AA | 20050526 | CA 2004-2544492 | 20041105 |
| US 2005137399 | A1 | 20050623 | US 2004-982757 | 20041105 |
| US 2005209247 | A1 | 20050922 | US 2004-982543 | 20041105 |
| EP 1699421 | A2 | 20060913 | EP 2004-816941 | 20041105 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR, IS, YU | | | | |

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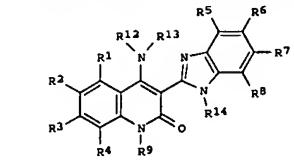
| PRIORITY APPLN. INFO.: | US 2003-517915P | P | 20031107 |
| | US 2003-526425P | P | 20031202 |
| | US 2003-526426P | P | 20031202 |
| | US 2004-546017P | P | 20040219 |
| | WO 2004-US36941 | W | 20041105 |

OTHER SOURCE(S): CASREACT 143:7709; MARPAT 143:7709
GI

L6 ANSWER 7 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)



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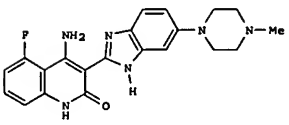


II

AB The title compds. I [R1-R4 = H, halo, CN, NO2, etc.; R5-R8 = H, halo, NO2, etc.; R9 = H; R12 = H, alkyl, aryl, heterocyclyl; R13 = H, alkyl, aryl, heterocyclyl, etc.; R14 = H] and their pharmaceutically acceptable lactate salts, useful for inhibiting vascular endothelial growth factor receptor tyrosine kinase, were prepared E.g., a multi-step synthesis of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one (II) and its lactate salt, starting from 5-chloro-2-nitroaniline and 1-methylpiperazine, was given. The pharmaceutically acceptable salts of I have improved aqueous solubility and desirable drug substance properties. Many of the exemplary compds. I displayed an IC50 of less than 10 μM with respect to Flt-1, KDR, PDGF, c-KIT, FLT-3, VEGFR1, VEGFR2, c-Met, CSF-1, FGFR3 and/or bFGFR. In addition, many of the exemplary compds. exhibited IC50 value of less than 10 μM with respect to PDGFR. The 4-amino substituted compds. I such as II were found to be potent inhibitors of various kinases such as VEGFR2 (KDR, Flk-1), PGFR1 and PDGFRβ with IC50's ranging from 10-27 nM. II inhibits FGFR3 receptor phosphorylation and ERK phosphorylation in multiple myeloma cell lines with activating FGFR3 mutations.

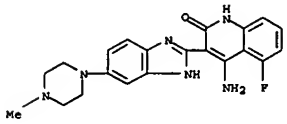
IT 692737-80-7P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzimidazole quinolinones and lactate salts thereof for inhibiting vascular endothelial growth factor receptor tyrosine kinase)

RN 692737-80-7 CA
CN Propanoic acid, 2-hydroxy-, compd. with 4-amino-5-fluoro-3-[5-(4-methyl-1-piperazinyl)-1H-benzimidazol-2-yl]-2(1H)-quinolinone (1:1) (9CI) (CA

L6 ANSWER 7 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)
INDEX NAME)

CM 1

CRN 405169-16-6
CMF C21 H21 F N6 O



CM 2

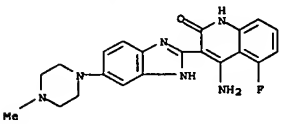
CRN 50-21-5
CMF C3 H6 O3

L6 ANSWER 8 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 141:1211 CA
TITLE: Methods of treating cancer with a methylpiperazinyl benzimidazolyl quinolinone and related methods
INVENTOR(S): Machajewski, Timothy D.; Hannah, Alison; Harwood, Eric; Haroldsen, Peter; Heise, Carla C.; Samara, Emil; Shang, Xiao; Vora, Jayesh; Zhu, Shuguang
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004043389 | A2 | 20040527 | WO 2003-US35806 | 20031112 |
| WO 2004043389 | A3 | 20040805 | | |
| WO 2004043389 | B1 | 20040916 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2501932 | AA | 20040527 | CA 2003-2501932 | 20031112 |
| AU 2003290699 | A1 | 20040603 | AU 2003-290699 | 20031112 |
| US 2004220196 | A1 | 20041104 | US 2003-706328 | 20031112 |
| EP 1565187 | A2 | 20050824 | EP 2003-783281 | 20031112 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003016229 | A | 20051004 | BR 2003-16229 | 20031112 |
| CN 1711088 | A | 20051221 | CN 2003-80103178 | 20031112 |
| JP 2006511616 | T2 | 20060406 | JP 2005-507133 | 20031112 |
| NO 2005002760 | A | 20050720 | NO 2005-2760 | 20050607 |
| PRIORITY APPLN. INFO.: | | | US 2002-426107P | P 20021113 |
| | | | US 2002-426204P | P 20021113 |
| | | | US 2002-426282P | P 20021113 |
| | | | US 2003-460328P | P 20030403 |
| | | | US 2003-460369P | P 20030403 |
| | | | US 2003-460493P | P 20030403 |
| | | | US 2003-517915P | P 20031107 |

L6 ANSWER 8 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)
WO 2003-US35806 W 20031112

AB Methods of treating cancer using 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (I) are provided. In particular, the methods are effective for the treatment of solid tumors or leukemias, including prostate, colorectal, breast, multiple myeloma, pancreatic, small cell carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, or myelo-proliferative disease. Further provided are methods of measuring the amount of I and determining a metabolic profile therefore. The growth of both the KM12L4a and MV4;11 xenografts in mice were potently inhibited by I in vivo.
IT 405169-16-6
RL: ANT (Analyte); BSU (Biological study, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); RCT (Reactant); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(cancer treatment with methylpiperazinyl benzimidazolyl quinolinone and related methods)
RN 405169-16-6 CA
CN 2(1H)-Quinolinone, 4-amino-5-fluoro-3-[5-(4-methyl-1-piperazinyl)-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)



L6 ANSWER 9 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 140:321363 CA
TITLE: Preparation of [(piperazinyl)benzimidazolyl]quinolinones and analogs as tyrosine kinase inhibitors for treatment of cancer
INVENTOR(S): Velaparthi, Upender; Wittman, Mark D.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004030620 | A2 | 20040415 | WO 2003-US30669 | 20030929 |
| WO 2004030620 | A3 | 20040610 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003275282 | A1 | 20040423 | AU 2003-275282 | 20030929 |
| US 2004092514 | A1 | 20040513 | US 2003-674098 | 20030929 |
| EP 1545529 | A2 | 20050629 | EP 2003-759558 | 20030929 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| PRIORITY APPLN. INFO.: | | | US 2002-415066P | P 20020930 |
| | | | WO 2003-US30669 | W 20030929 |

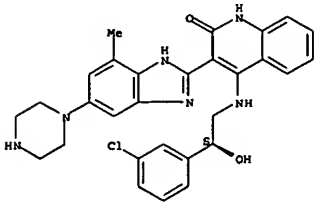
OTHER SOURCE(S): MARPAT 140:321363
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I and II [wherein A, B, D, and E = independently C, N, O, S or a direct bond, provided that not more than one of A, B, D, and E can be a single bond; Y = O or S; W = N, CH, O, and S, provided that when W = O or S, R7 is absent; R1-R7 = independently H, alkyl, alkenyl, alkynyl, (hetero)cycloalkyl, halo, amino(alkyl), (thio)alkoxy, NO2, (hetero)aryl, (thio)alkoxyalkyl, aminoalkyl, (hetero)aralkyl, heterocycloalkylalkyl, CN, CO2R8, CONR9R10, CO2NR11R12, NR13CONR14R15, NR16SO2R17, SO2NR18R19, C(NR20)NR21R22, NHZ, or NH2-(hetero)aryl; Z = (un)substituted (cyclo)alkyl, (cyclo)alkenyl, or alkynyl, optionally interrupted by CO, CONH, CNOR26, CNNR27, CNNCOR28, or CNNSO2R29; R8-R24 and R26 = independently H, alkyl, alkenyl, alkynyl, cycloalkyl(alkyl), OH, alkoxy, (hetero)aryl, heterocyclyl, heteroarylalkyl, alkyl-R25; R25 = alkenyl, ...

L6 ANSWER 9 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)
SH, (thio)alkoxy, NH2, (di)alkylamino, (hetero)aryl, CN, halo, heterocyclyl, sulfoxy, sulfonyl, NR27CO2R28, NR29COR30, NR31SO2R32, SO2NR31R32, or CONR33R34; R27-R34 = independently H, or (cyclo)alkyl; and enantiomers, diastereomers, pharmaceutically acceptable salts, hydrates, prodrugs, or solvates thereof] were prepd. as tyroaine kinase inhibitors. For example, 1-[4-(3,4-diamino-5-methylphenyl)piperazin-1-yl]ethanone was condensed with 2,4-dichloroquinoline-3-carboxaldehyde in MeOH to give the benzimidazole. Hydrolysis of the chloro group using 4N HCl in dioxane afforded the 2-4-quinolinones. Nucleophilic addn. of (S)-2-(3-chlorophenyl)-2-hydroxyethylamine using N-methylmorpholine in DMF provided III and IV. Compds. of the invention exhibited kinase activity of <25 μM against one or more of the following kinases: CDK, EMT, FAK, Her1, Her2, IGF, IR, LCK, MET, PDGF, VEGF. Thus, I, II, and their pharmaceutical comps. are useful as for treatment of cancer and other diseases that can be treated by inhibiting tyrosine kinase enzymes (no data).
IT 677341-90-1P, 4-[[[(S)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-3-[4-methyl-6-(piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(tyrosine kinase inhibitor; preparation of [(piperazinyl)benzimidazolyl]quinolinones and analogs as tyrosine kinase inhibitors for treatment of cancer)
RN 677341-90-1 CA
CN 2(1H)-Quinolinone, 4-[[[(2S)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-[4-methyl-6-(1-piperazinyl)-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 10 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 140:235711 CA
TITLE: Preparation of benzimidazole quinolinones for inhibiting a serine/threonine kinase
INVENTOR(S): Barsanti, Paul A.; Bussiere, Dirksen; Harrison, Stephen D.; Heise, Carla C.; Jansen, Johanna M.; Jazan, Elisa; Machajewski, Timothy D.; Mcbride, Christopher; McCrea, William R.; Ng, Simon; Ni, Zhi-Jie; Pecchi, Sabina; Pfister, Keith; Ramurthy, Savithri; Renhowe, Paul A.; Shafer, Cynthia M.; Silver, Joel B.; Wagman, Allan; Weismann, Marion
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 570 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004018419 | A2 | 20040304 | WO 2003-US25990 | 20030819 |
| WO 2004018419 | A3 | 20040603 | | |
| WO 2004018419 | B1 | 20040729 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
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| EP 1539754 | A2 | 20050615 | EP 2003-781286 | 20030819 |
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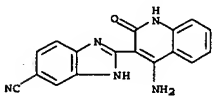
| BR 2003013743 | A | 20050705 | BR 2003-13743 | 20030819 |
| CN 1692112 | A | 20051102 | CN 2003-824565 | 20030819 |
| JP 2006503919 | T2 | 20060202 | JP 2005-501762 | 20030819 |

PRIORITY APPLN. INFO.: US 2002-405729P P 20020823
US 2002-426107P P 20021113
US 2002-426226P P 20021113
US 2002-426282P P 20021113
US 2002-428210P P 20021121
US 2003-460327P P 20030403
US 2003-460328P P 20030403

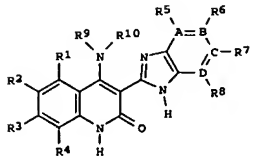
L6 ANSWER 10 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)
VEGFR2, VEGFR3, FGFR1, FGFR3, c-Kit, c-ABL, FLT-3, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, MEK1, CHK2, Fyn, Lck, Rsk2, PAR-1, PDGFRα, and PDGFRβ with IC50 values of less than 1 μM.
IT 405168-20-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of benzimidazole quinolinones for inhibiting a serine/threonine kinase)
RN 405168-20-9 CA
CN 1H-Benzimidazole-5-carbonitrile, 2-(4-amino-1,2-dihydro-2-oxo-3-quinolinyl)- (9CI) (CA INDEX NAME)



L6 ANSWER 10 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)

| | | |
|---|---|---|
| US 2003-460493P | P | 20030403 |
| US 2003-478916P | P | 20030616 |
| US 2003-484048P | P | 20030701 |
| WO 2003-US25990 | W | 20030819 |

OTHER SOURCE(S): MARPAT 140:235711
GI



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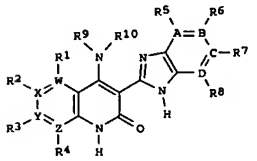

II

AB The title compds. [I and II; A, B, C, and D = C, N; W, X, Y and Z = C, N and at least one of W, X, Y, and Z = N; R1-R8 = H, halo, CN, NO2, etc.; R9 = H, (un)substituted alkyl, aryl, etc.; R10 = H; or NR9R10 = 5-7 membered ring], useful for inhibiting various enzymes and treating various conditions, were prepared E.g., a multi-step synthesis of 4-amino-3-(benzimidazol-2-yl)-6-(4-methylpiperazinyl)hydroquinolin-2-one, was given. The majority of the exemplary compds. I displayed an IC50 of less than 10 μM with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, Fyn, Lck, Rsk2, PAR-1, c-Kit, c-ABL, p60src, PGFR3, FLT-3, PDGFRα, and PDGFRβ. In addition, many of the exemplary compds. exhibited IC50 values in the nM range and show potent activity with respect to VEGFR1,

L6 ANSWER 11 OF 12 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 138:153534 CA
TITLE: Preparation of benzimidazolyl-substituted quinolinone derivatives and analogs, with inhibitory action against vascular endothelial growth factor receptor tyrosine kinase, and useful as anticancer agents
INVENTOR(S): Renhowe, Paul A.; Pecchi, Sabina; Machajewski, Timothy D.; Shafer, Cynthia M.; Taylor, Clarke; McCrea, William R.; McBride, Christopher; Jazan, Elisa
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 69 pp., Cont.-in-part of U.S. Pat. Appl. 2002 107,392.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003028018 | A1 | 20030206 | US 2002-116117 | 20020405 |
| US 2002107392 | A1 | 20020808 | US 2001-951265 | 20010911 |
| US 6605617 | B2 | 20030812 | | |
| EP 1650203 | A1 | 20060426 | EP 2005-17665 | 20010911 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2003158224 | A1 | 20030821 | US 2002-284017 | 20021030 |
| US 6774237 | B2 | 20040810 | | |
| US 2004006101 | A1 | 20040108 | US 2003-387355 | 20030312 |
| US 6762194 | B2 | 20040713 | | |
| CA 2481055 | AA | 20031023 | CA 2003-2481055 | 20030404 |
| WO 2003087095 | A1 | 20031023 | WO 2003-US10463 | 20030404 |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003226275 | A1 | 20031027 | AU 2003-226275 | 20030404 |
| EP 1497287 | A1 | 20050119 | EP 2003-746614 | 20030404 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003008996 | A | 20050222 | BR 2003-8996 | 20030404 |
| CN 1659165 | A | 20050824 | CN 2003-812909 | 20030404 |
| JP 2005527587 | T2 | 20050915 | JP 2003-584051 | 20030404 |
| US 2004097545 | A1 | 20040520 | US 2003-413411 | 20030703 |
| US 6800760 | B2 | 20041005 | | |
| US 2005054672 | A1 | 20050310 | US 2004-886950 | 20040708 |
| NO 2004004776 | A | 20041207 | NO 2004-4776 | 20041103 |
| US 2005209456 | A1 | 20050922 | US 2005-92137 | 20050329 |

PRIORITY APPLN. INFO.: US 2000-232159P P 20000911
US 2001-951265 A2 20010911

L6 ANSWER 11 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)

| | | |
|---|---|---|
| EP 2001-973722 | A3 | 20010911 |
| US 2002-116117 | A | 20020405 |
| US 2002-284017 | A1 | 20021030 |
| WO 2003-US10463 | W | 20030404 |
| US 2004-886950 | A1 | 20040708 |

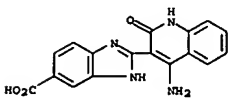
OTHER SOURCE(S): MARPAT 138:153534
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. of formulas I and II are provided [for I: Z = O, S, (un)substituted NH; Y = certain OH derivs., CHO, esters and amides of CO2H, certain NH2 derivs.; R1-R4 = H, halo, cyano, NO2, OH or derivs., NH2 or derivs., (un)substituted amidinyl, guanidinyl, alk(en/yn)yl, aryl, heterocyclyl, CHO, CO2H and esters and amides; R5-R8 = H, halo, NO2, OH or derivs., NH2 or derivs., SH or derivs., cyano, etc.; R9 = H, OH, (un)substituted alkoxy or aryloxy, NH2 or derivs., (un)substituted alkyl or aryl, CHO, alkanoyl, aroyl; for II: A, B, D, E = C or N, with at least one being N; Y = H, OH or derivs., SH or derivs., NH2 or derivs., cyano, various acyl groups, (un)substituted alk(en/yn)yl, aralkyl, heterocycloalkyl, aryl, etc.; R1-R8 = H, halo, NO2, cyano, OH or derivs., NH2 or derivs., acyl, SH or derivs., etc.; R9 = H, OH, (un)substituted alkoxy, aryloxy, NH2 or derivs., aryl, CHO, alkanoyl, aroyl]. Also provided are pharmaceutical formulations including the compds. or their pharmaceutically acceptable salts and a pharmaceutically acceptable carrier, which may be prepared by mixing the compds. or salts with a carrier and water. A disclosed method of treating a patient includes administering a pharmaceutical formulation according to the invention to a patient. Claims include tautomers of the compds., pharmaceutically acceptable salts, and pharmaceutically acceptable salts of the tautomers. I and II are inhibitors of receptor tyrosine kinases, and particularly of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase. As such, they are inhibitors of angiogenesis, and thereby act as anticancer agents. Approx 270 invention compds. are listed, with detailed prepns. given for about 50 compds. Several general preparatory methods are discussed in detail. For instance, cyclocondensation of Et 2-(benzimidazol-2-yl)acetate with the corresponding ortho-amino nitrile (prepns. given), carried out in refluxing ClCH2CH2Cl in the presence of SnCl4, gave the invention quinolinone III. Many compds. I and II had in vitro IC50 values of less than 10 μM with respect to flt-1 (VEGFR1), KDR (VEGFR2) and bFGF kinases (recombinant, expressed in Sf9 insect cells).

IT 405168-78-7P, 2-(4-Amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-6-carboxylic acid
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; prepn. of benzimidazolyl-substituted quinolinone derivs. and analogs as VEGFR tyrosine kinase -inhibiting anticancer agents)

RN 405168-78-7 CA
CN 1H-Benzimidazole-5-carboxylic acid, 2-(4-amino-1,2-dihydro-2-oxo-3-quinolinyl)- (9CI) (CA INDEX NAME)



L6 ANSWER 12 OF 12 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 136:263158 CA
TITLE: Benzimidazolyl-substituted quinolinone derivatives and analogs, with inhibitory action against vascular endothelial growth factor receptor tyrosine kinase, and useful as anticancer agents
INVENTOR(S): Renhowe, Paul; Pecchi, Sabina; Machajewski, Tim; Shafer, Cynthia; Taylor, Clarke; McCrea, Bill; McBride, Chris; Jazan, Elisa; Wernette-Hammond, Mary-Ellen; Harris, Alex
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 207 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002022598 | A1 | 20020321 | WO 2001-US42131 | 20010911 |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2421120 | AA | 20020321 | CA 2001-2421120 | 20010911 |
| AU 2001093275 | A5 | 20020326 | AU 2001-93275 | 20010911 |
| EP 1317442 | A1 | 20030611 | EP 2001-973722 | 20010911 |
| EP 1317442 | B1 | 20051116 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 2001013757 | A | 20040302 | BR 2001-13757 | 20010911 |
| JP 2004509112 | T2 | 20040325 | JP 2002-526851 | 20010911 |
| NZ 524717 | A | 20040924 | NZ 2001-524717 | 20010911 |
| AT 309996 | E | 20051215 | AT 2001-973722 | 20010911 |
| ES 2250480 | T3 | 20060416 | ES 2001-1973722 | 20010911 |
| EP 1650203 | A1 | 20060426 | EP 2005-17665 | 20010911 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| ZA 2003001578 | A | 20040826 | ZA 2003-1578 | 20030226 |
| NO 2003001097 | A | 20030325 | NO 2003-1097 | 20030310 |
| US 2004006101 | A1 | 20040108 | US 2003-387355 | 20030312 |
| US 6762194 | B2 | 20040713 | | |
| BG 107709 | A | 20040130 | BG 2003-107709 | 20030408 |
| HK 1053644 | A1 | 20060504 | HK 2003-104217 | 20030612 |
| US 2005054672 | A1 | 20050310 | US 2004-886950 | 20040708 |
| US 2005209456 | A1 | 20050922 | US 2005-92137 | 20050329 |
| AU 2005202068 | A1 | 20050602 | AU 2005-202068 | 20050513 |
| PRIORITY APPLN. INFO.: | | | US 2000-232159P | P 20000911 |
| | | | AU 2001-293275 | A3 20010911 |
| | | | EP 2001-973722 | A3 20010911 |
| | | | US 2001-951265 | A1 20010911 |
| | | | WO 2001-US42131 | W 20010911 |
| | | | US 2002-284017 | A1 20021030 |
| | | | US 2004-886950 | A1 20040708 |

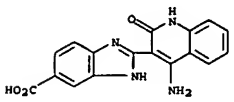
OTHER SOURCE(S): MARPAT 136:263158
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. of formulas I and II are provided [for I: Z = O, S, (un)substituted NH; Y = certain OH derivs., CHO, esters and amides of CO2H, certain NH2 derivs.; R1-R4 = H, halo, cyano, NO2, OH or derivs., NH2 or derivs., (un)substituted amidinyl, guanidinyl, alk(en/yn)yl, aryl, heterocyclyl, CHO, CO2H and esters and amides; R5-R8 = H, halo, NO2, OH or derivs., NH2 or derivs., SH or derivs., cyano, etc.; R9 = H, OH, (un)substituted alkoxy or aryloxy, NH2 or derivs., (un)substituted alkyl or aryl, CHO, alkanoyl, aroyl; for II: A, B, D, E = C or N, with at least one being N; Y = H, OH or derivs., SH or derivs., NH2 or derivs., cyano, various acyl groups, (un)substituted alk(en/yn)yl, aralkyl, heterocycloalkyl, aryl, etc.; R1-R8 = H, halo, NO2, cyano, OH or derivs., NH2 or derivs., acyl, SH or derivs., etc.; R9 = H, OH, (un)substituted alkoxy, aryloxy, NH2 or derivs., aryl, CHO, alkanoyl, aroyl]. Also provided are pharmaceutical formulations including the compds. or their pharmaceutically acceptable salts and a pharmaceutically acceptable carrier, which may be prepared by mixing the compds. or salts with a carrier and water. A disclosed method of treating a patient includes administering a pharmaceutical formulation according to the invention to a patient. Claims include tautomers of the compds., pharmaceutically acceptable salts, and pharmaceutically acceptable salts of the tautomers. I and II are inhibitors of receptor tyrosine kinases, and particularly of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase. As such, they are inhibitors of angiogenesis, and thereby act as anticancer agents. Approx 270 invention compds. are listed, with detailed prepns. given for about 50 compds. Several general preparatory methods are discussed in detail. For instance, cyclocondensation of Et 2-(benzimidazol-2-yl)acetate with the corresponding ortho-amino nitrile (prepns. given), carried out in refluxing ClCH2CH2Cl in the presence of SnCl4, gave the invention quinolinone III. Many compds. I and II had in vitro IC50 values of less than 10 μM with respect to flt-1 (VEGFR1), KDR (VEGFR2) and bFGF kinases (recombinant, expressed in Sf9 insect cells).

IT 405168-78-7P, 2-(4-Amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-6-carboxylic acid
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of benzimidazolyl-substituted quinolinone derivs. and analogs as VEGFR tyrosine kinase

L6 ANSWER 12 OF 12 CA COPYRIGHT 2006 ACS on STN (Continued)
-inhibiting anticancer agents)
RN 405168-78-7 CA
CN 1H-Benzimidazole-5-carboxylic acid, 2-(4-amino-1,2-dihydro-2-oxo-3-quinolinyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
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L7             7 L4 NOT L6

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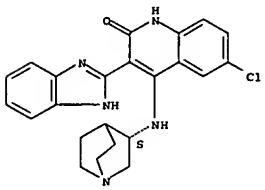
L7 ANSWER 1 OF 7 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 145:124498 CA
TITLE: 4-(Aminoalkylamino)-3-benzimidazole-quinolinones as potent CHK-1 inhibitors
AUTHOR(S): Ni, Zhi-Jie; Barsanti, Paul; Brammeier, Nathan; Diebes, Anthony; Poon, Daniel J.; Ng, Simon; Pecchi, Sabina; Pfister, Keith; Renhowe, Paul A.; Ramurthy, Savithri; Wagman, Allan S.; Bussiere, Dirksen E.; Le, Vincent; Zhou, Yasheen; Jansen, Johanna M.; Ma, Sylvia; Gesner, Thomas G.
CORPORATE SOURCE: Chiron Corporation, Emeryville, CA, 94608, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(12), 3121-3124
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CHK-1 is one of the key enzymes regulating checkpoints in cellular growth cycles. Novel 4-(aminoalkylamino)-3-benzimidazolyl-2-quinolinones were prepared and assayed for their ability to inhibit CHK-1. These compds. are potent cell permeable CHK-1 inhibitors and showed a synergistic effect with a DNA-damaging agent, camptothecin.
IT 405168-58-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of 4-(aminoalkylamino)-3-benzimidazolyl-2-quinolinones as potent CHK-1 inhibitors with synergistic effect with a DNA-damaging agent (camptothecin))
RN 405168-58-3 CA
CN 2(1H)-Quinolinone, 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benzimidazol-2-yl)-6-chloro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 7 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 144:267266 CA
TITLE: Flt3 inhibitors for immune suppression
INVENTOR(S): Small, Donald; Whartenby, Katherine A.; Pardoll, Drew
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2006020145 | A2 | 20060223 | WO 2005-US25318 | 20050714 |

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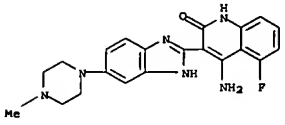
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-589511P P 20040719

OTHER SOURCE(S): MARPAT 144:267266
AB New methods are provided for suppressing the immune system and for treating immune related disorders. Therapies of the invention include administration of an FLT3 inhibitor compound to a subject in need thereof, such as a subject suffering from organ rejection, bone marrow transplant rejection, acquired immune deficiency syndrome, arthritis, aplastic anemia, graft-vs.-host disease, Graves' disease, established exptl. allergic encephalitomyelitis, multiple sclerosis, lupus, or a neurol. disorder. Methods are also provided for screening therapeutic agents for treating immune disorders, including the use of a mouse having an elevated level of FLT3 receptor activity.
IT 405169-16-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Flt3 inhibitors for immune suppression by treating cells for therapy of immune or neurol. disorders)
RN 405169-16-6 CA
CN 2(1H)-Quinolinone, 4-amino-5-fluoro-3-[5-(4-methyl-1-piperazinyl)-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)

L7 ANSWER 2 OF 7 CA COPYRIGHT 2006 ACS on STN (Continued)



L7 ANSWER 3 OF 7 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:477966 CA
TITLE: Preparation of benzimidazole quinolinones for inhibiting a checkpoint kinase 1 and their use in combination therapy for cancer
INVENTOR(S): Gesner, Thomas G.; Barsanti, Paul A.; Harrison, Stephen D.; Ni, Zhi-Jie; Brammeier, Nathan M.; Zhou, Yasheen; Le, Vincent P.
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 249 pp., Cont.-in-part of U.S. Ser. No. 644,055.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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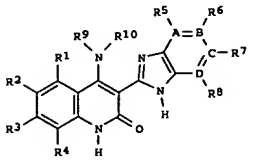
| US 2005256157 | A1 | 20051117 | US 2005-41191 | 20050121 |
| US 2004092535 | A1 | 20040513 | US 2003-644055 | 20030819 |
| CN 1692112 | A | 20051102 | CN 2003-824565 | 20030819 |
| US 2005203101 | A1 | 20050915 | US 2004-839793 | 20040505 |

PRIORITY APPLN. INFO.: US 2002-405729P P 20020823
US 2002-426107P P 20021113
US 2002-426226P P 20021113
US 2002-426282P P 20021113
US 2002-428210P P 20021121
US 2003-460327P P 20030403
US 2003-460328P P 20030403
US 2003-460493P P 20030403
US 2003-478916P P 20030616
US 2003-484048P P 20030701
US 2003-644055 A2 20030819
US 2004-538984P P 20040123

OTHER SOURCE(S): MARPAT 143:477966
GI

L7 ANSWER 3 OF 7 CA COPYRIGHT 2006 ACS on STN (Continued)



I

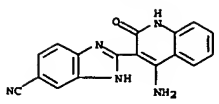
AB The title compds. [I; A, B, C, D = C, N; R1 = H, halo, CN, NO2, etc.; R2, R3 = H, halo, NO2, CN, etc.; R4 = H, (un)substituted alkyl; R5, R8 = H, (un)substituted alkyl, alkenyl, heterocyclyl; or R5 may be absent if A = N; or R8 may be absent if D = N; R6, R7 = H, halo, NO2, CN, etc.; R9 = H, (un)substituted alkyl, aryl, etc.; R10 = H; or R9 and R10 join together to form one or more rings, each having 5-7 members], useful for inhibiting checkpoint kinase 1, inducing cell cycle progression, and increasing apoptosis in cells, were prepared E.g., a multi-step synthesis of 4-amino-3-(benzimidazol-2-yl)-6-(4-methylpiperazinyl)hydroquinolin-2-one, was given. The compds. I were tested against various kinases. Two of the prepared compds. I, 4-[(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]-3-(1H-benimidazol-2-yl)-6-chloroquinolin-2-(1H)-one and 6-chloro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-4-[(piperidin-2-ylmethyl)amino]quinolin-2(1H)-one, were found to be potent inhibitors of CHK1 with IC50 of 0.32 nM and 0.63 nM, resp. The majority of the exemplary compds. I displayed an IC50 of less than 10 μM with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, Fyn, Lck, Rsk2, PAR-1, c-Kit, c-ABL, p60src, FGFR3, FLT-3, PDGFRα, and PDGFRβ. In addition, many of the exemplary compds. exhibited IC50 values in the nM range and show potent activity with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR3, c-Kit, c-ABL, FLT-3, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, MEK1, CHK2, Fyn, Lck, Rsk2, PAR-1, PDGFRα, and PDGFRβ with IC50 values of less than 1 μM. The compds. I may be used to prepare pharmaceutical compns. and may be used in conjunction with DNA damaging agents.

IT 405168-20-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of benzimidazole quinolinones for inhibiting a checkpoint kinase 1 and their use in combination therapy for cancer)

RN 405168-20-9 CA

CN 1H-Benzimidazole-5-carbonitrile, 2-(4-amino-1,2-dihydro-2-oxo-3-quinolinyl)- (9CI) (CA INDEX NAME)

L7 ANSWER 3 OF 7 CA COPYRIGHT 2006 ACS on STN (Continued)



L7 ANSWER 4 OF 7 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 143:59842 CA
TITLE: Preparation of quinolinone derivatives as protein kinase inhibitors
INVENTOR(S): Liang, Congxin
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005054183 | A2 | 20050616 | WO 2004-US40148 | 20041201 |
| WO 2005054183 | A3 | 20050929 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-525945P P 20031201
US 2004-545721P P 20040218

OTHER SOURCE(S): MARPAT 143:59842
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = H, halo, alkyl, etc.; R2 = H, halo, alkyl, etc.; R3 = H, alkyl, halo, etc.; R4 = H, alkyl; R5 = H, alkyl, hydroxy; R6 = hydroxy, alkoxy, cycloalkoxy, etc.; n, m = 0-2; p = 1-3; X = CR9, N; R9 = H, halo, alkyl; L = O, NR10, CONR10, etc.; R10 = H, alkyl] and their pharmaceutically acceptable salts were prepared For example, EDCI mediated amidation of compound II, e.g., prepared from Et cyanoacetate in 4 steps, with ((4R,6S)-6-aminomethyl-2,2-dimethyl-[1,3]-dioxan-4-yl)acetic acid tert-Bu ester followed by treatment with aqueous HCl and hydrolysis using NaOH afforded the sodium salt of compound III. In VEGFR biochem. assays, compds. I exhibited IC50 between 1 - 5000 nM. Compds. I are claimed useful as protein kinase inhibitors.

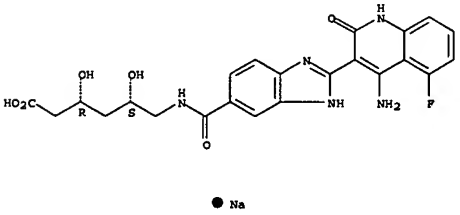
IT 853880-97-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of quinolinone derivs. as protein kinase inhibitors)

RN 853880-97-4 CA

L7 ANSWER 4 OF 7 CA COPYRIGHT 2006 ACS on STN (Continued)

CN D-erythro-Hexonic acid, 6-[[[2-(4-amino-5-fluoro-1,2-dihydro-2-oxo-3-quinolinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-2,4,6-trideoxy-, monosodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● Na

L7 ANSWER 5 OF 7 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:53554 CA
TITLE: Advanced quinolinone based protein kinase inhibitors
INVENTOR(S): Liang, Congxin
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005053692 | A1 | 20050616 | WO 2004-US40346 | 20041201 |

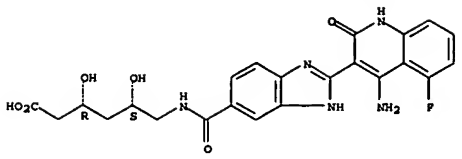
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-525945P P 20031201
US 2004-545721P P 20040218

OTHER SOURCE(S): MARPAT 143:53554
AB Hydroxy carboxy quinolinone based derivs. have enhanced and unexpected drug properties as inhibitors of protein kinases and are useful in treating disorders related to abnormal protein kinase activities such as cancer.
IT 853880-97-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(advanced quinolinone based protein kinase inhibitors for treatment of disorders)
RN 853880-97-4 CA
CN D-erythro-Hexonic acid, 6-[[[2-(4-amino-5-fluoro-1,2-dihydro-2-oxo-3-quinolinyl)-1H-benzimidazol-5-yl]carbonyl]amino]-2,4,6-trideoxy-, monosodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L7 ANSWER 5 OF 7 CA COPYRIGHT 2006 ACS on STN (Continued)



● Na

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 7 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:7732 CA
TITLE: Process for preparation of benzimidazolylquinolones by reaction of aminobenzonitriles with benzimidazolylacetates.
INVENTOR(S): Cai, Shaopei; Chou, Joyce; Harwood, Eric; Ryckman, David; Shang, Xiao; Zhu, Shuguang; Machajewski, Timothy D.
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005046590 | A2 | 20050526 | WO 2004-US37051 | 20041105 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

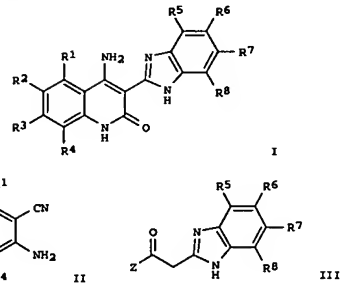
| | | | | |
|---|---|---|---|---|
| AU 2004288709 | A1 | 20050526 | AU 2004-288709 | 20041105 |
| CA 2543820 | AA | 20050526 | CA 2004-2543820 | 20041105 |
| US 2005137399 | A1 | 20050623 | US 2004-982757 | 20041105 |
| US 2005209247 | A1 | 20050922 | US 2004-982543 | 20041105 |
| EP 1682529 | A2 | 20060726 | EP 2004-810468 | 20041105 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS

PRIORITY APPLN. INFO.: US 2003-517915P P 20031107
US 2003-526425P P 20031202
US 2003-526426P P 20031202
US 2004-546017P P 20040219
WO 2004-US37051 W 20041105

OTHER SOURCE(S): CASREACT 143:7732; MARPAT 143:7732
GI

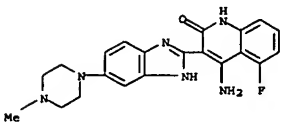
L7 ANSWER 6 OF 7 CA COPYRIGHT 2006 ACS on STN (Continued)



I II III

AB Title compds. [I; R1-R4 = H, Cl, Br, F, iodo, OR10, NR11R12, (substituted) alkyl, aryl, alkenyl, alkynyl, heterocyclyl, heterocyclylalkyl; R5-R8 = H, F, Cl, Br, iodo, OR13, NR14R15, SR16, (substituted) alkyl, aryl, alkenyl, alkynyl, heterocyclyl, heterocyclylalkyl, alkoxyalkyl, aryloxyalkyl, heterocyclyloxyalkyl; R10, R13 = (substituted) alkyl, aryl, heterocyclyl, heterocyclylalkyl, alkoxyalkyl, aryloxyalkyl, heterocyclyloxyalkyl; R11-R16 = (substituted) alkyl, aryl, heterocyclyl], were prepared by reaction of aminobenzonitriles (II; R1-R4 as above) with benzimidazolylacetates (III; R5-R8 as above; Z = OR9a, NR9bR9c; R9a-R9c = alkyl] in the presence of the Na or K salt of a base. Thus, Et [6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]acetate (preparation given), 2-amino-6-fluorobenzonitrile, and potassium bis(trimethylsilyl)amide were stirred together in THF at 40-62° for 1 h to give 47.9% 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one.
IT 405169-16-6P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzimidazolylquinolones by reaction of aminobenzonitriles with benzimidazolylacetates)
RN 405169-16-6 CA
CN 2(1H)-Quinolinone, 4-amino-5-fluoro-3-[5-(4-methyl-1-piperazinyl)-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)

L7 ANSWER 6 OF 7 CA COPYRIGHT 2006 ACS on STN (Continued)



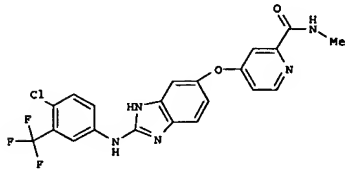
L7 ANSWER 7 OF 7 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 141:343478 CA
TITLE: Use of small molecule compounds for immunopotentiation
INVENTOR(S): Valiante, Nicholas
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 146 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004087153 | A2 | 20041014 | WO 2004-US10331 | 20040329 |
| WO 2004087153 | A3 | 20050317 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2520124 | AA | 20041014 | CA 2004-2520124 | 20040329 |
| US 2005136065 | A1 | 20050623 | US 2004-814480 | 20040329 |
| EP 1608369 | A2 | 20051228 | EP 2004-758593 | 20040329 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK | | | | |

PRIORITY APPLN. INFO.: US 2003-458888P P 20030328
WO 2004-US10331 W 20040329

OTHER SOURCE(S): MARPAT 141:343478
GI



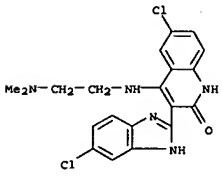
I

L7 ANSWER 7 OF 7 CA COPYRIGHT 2006 ACS on STN (Continued)

AB The invention provides immunostimulatory compns. comprising a small mol. immunopotentiator (SMIP) compound and methods of administration thereof. Also provided are methods of administering a SMIP compound in an effective amount to enhance the immune response of a subject to an antigen. Further provided are compns. and methods of administering SMIP compds. alone or in combination with another agent for the treatment of cancer, infectious diseases and/or allergies/asthma. Preparation of selected compds., e.g. I, is included.

IT 668429-57-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small mol. compds. for immunopotentiation)

RN 668429-57-0 CA
CN 2(1H)-Quinolinone, 6-chloro-3-(5-chloro-1H-benzimidazol-2-yl)-4-[[2-(dimethylamino)ethyl]amino]- (9CI) (CA INDEX NAME)



=> d ibib abs 1-50

L13 ANSWER 1 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 144:35080 CA
TITLE: Preventing or treating cutaneous inflammation and hyperpigmentation by inhibiting the stem cell factor signaling pathway
INVENTOR(S): Longley, B. Jack
PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, USA
SOURCE: U.S., 25 pp., Cont.-in-part of U.S.Ser. No 474,478.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6977159 | B1 | 20051220 | US 2002-980572 | 20020923 |
| US 6576812 | B1 | 20030610 | US 1999-306143 | 19990506 |
| US 2002123031 | A1 | 20020905 | US 1999-474478 | 19991229 |
| US 6989248 | B2 | 20060124 | | |
| WO 2000067794 | A1 | 20001116 | WO 2000-US12405 | 20000505 |

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W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-306143 A2 19990506
US 1999-474478 A2 19991229
WO 2000-US12405 W 20000505

AB This invention provides a method of preventing or treating in a subject contact dermatitis which comprises adminiatering to the subject an amount of a compound capable of inhibiting the stem cell factor signaling pathway effective to prevent or treat contact dermatitis so as to thereby prevent or treat contact dermatitis in the subject. In human skin, Stem Cell Factor is produced by epidermal keratinocytes after birth, unlike in normal murine skin. The result of this, among other things, is that melanocytes are present in the interadnexal epidermis in human skin. In contrast, melanocytes in adult murine skin are generally confined to hair follicles, with the exception of rare epidermal melanocytes found in the ears, footpads, and tail. A few dermal melanocytes may also be found in mice, mostly in the ears. These differences have compromised the use of the mice as a model system for investigation of human cutaneous biol. It has been discovered that melanocyte migration and development, as well as the survival of melanocytes and mast cells, are dependent on expression of the kit protein, a receptor tyrosine kinase encoded by the c-kit protooncogene. The ligand for kit, known as stem cell factor (SCF) (also called mast cell growth factor, steel factor, and kit ligand) may be produced locally in human skin by epidermal keratinocytes, fibroblasts, and endothelial cells. The results presented here show that SCF expression by murine epidermal keratinocytes causes the maintenance and stimulation of epidermal melanocytes throughout life. These data support the hypothesis that the decrease in melanocyte nos. in the postnatal mouse epidermis is due to a lack of local SCF expression. The fact that SCF transgenic mice have greater responses to allergic and irritant contactants shows that epidermal SCF can actively contribute to eczematous dermatitis. This interpretation is confirmed by our demonstration that the inflammation can be diminiahed by blocking the SCF receptor with the ACK2 monoclonal antibody. Since human post natal epidermal keratinocytes express SCF, unlike post natal murine epidermal keratinocytea, and alterations of human epidermal SCF are found in spongiotic dermatitis (a form of eczema), these observations also support our contention that the skin of mice expressing epidermal SCF is a better model of human skin than is the skin of normal mice. Further supporting this claim is our previous observation of increased sol. epidermal SCF in the hyperpigmented lesions of mastocytoais. In sum, these data support our claim that animals expressing epidermal SCF are more suitable for a wide variety of investigations than those which do not. The inventors conclude that inhibition of the SCF-KIT signaling pathway has a beneficial effect in treating human dermatitis of the irritant and DTH types.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 139:292260 CA
TITLE: Preparation of 4-aminopyrrolopyrimidines as protein kinase inhibitors
INVENTOR(S): Calderwood, David; Arnold, Lee; Mazdiyasni, Hormoz; Hirst, Gavin C.; Deng, Bojuan B.; Johnston, David N.; Rafferty, Paul; Tometzki, Gerald B.; Twigger, Helen L.; Munschauer, Rainer
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 93 pp., Cont.-in-part of U.S. 6,001,839.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003187001 | A1 | 20031002 | US 1999-399083 | 19990917 |
| US 6001839 | A | 19991214 | US 1998-42702 | 19980317 |

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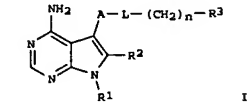
PRIORITY APPLN. INFO.: US 1998-42702 A2 19980317
US 1998-100954P P 19980918

OTHER SOURCE(S): MARPAT 139:292260
GI



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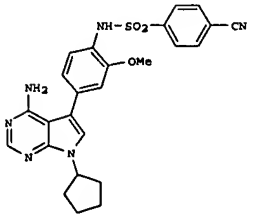

II

AB 7H-Pyrrolo[2,3-d]pyrimidin-4-amines [I; A = (un)substituted 6-membered arom. ring or 5- or 6-membered heteroarom. ring; L = RbNRSO2, RbNRP(O), or RbNRP(O)O, where Rb = alkylene group which when taken together with the sulfonamide, phosphinamide or phosphonamide group to which it is bound forms a 5- or 6-membered ring fused to ring A, or L = O, S, NR, 5-7 membered (oxa)azaphosphaarom. or (oxa)azaphosphacycloalkyl ring, or a variety of linkers contg. functional groups; R = H, acyl, or (un)substituted aliph., (hetero)arom., or cycloalkyl; R1 = H, 2-Ph-1,3-dioxan-5-yl or (un)substituted (cyclo)alkyl, cycloalkenyl, or phenylalkyl; R2 = H, halo, OH, CN, (un)subatituted aliph., cycloalkyl, (hetero)arom., (hetero)aralkyl, amino, or amido; R3 = (un)substituted aliph., alkenyl, (hetero)cycloalkyl, or (hetero)arom.; n = 0-6], and physiol. acceptable salts and metabolites thereof, were prepd. For example, II was prepd. in a 6-step sequence involving: (1) amine protection of 4-bromo-2-methoxyaniline with di-tert-Bu dicarbonate, (2) 4-addn. of diboron pinacol ester, (3) 4-substitution with 4-chloro-7-cyclopentyl-5-iodo-7H-pyrrolo[2,3-d]pyrimidine, (4) deprotection of the amine with F3CCO2H, (5) 4-amination of the pyrrolopyrimidine, and (6) amidation of the aniline with 4-cyanobenzenesulfonyl chloride. I inhibit serine/threonine and tyrosine kinase activity, affecting immunol., hyperproliferative, and angiogenic processes. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concns. of ≤ 50 μM, and some significantly inhibited cdc2 at concns. of 50 ≤ μM. Thus, these compds. are useful in the treatment of cancer and hyperproliferative disorders, rheumatoid arthritis, disorders of the immune system, transplant rejections, and inflammatory disordera.

L13 ANSWER 3 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 139:180075 CA
TITLE: Preparation of pyrrolopyrimidines as tyrosine kinase inhibitors
INVENTOR(S): Hirst, Gavin C.; Calderwood, David; Munschauer, Rainer; Arnold, Lee D.; Johnston, David N.; Rafferty, Paul
PATENT ASSIGNEE(S): Abbott GmbH & Co. KG, USA
SOURCE: U.S. Pat. Appl. Publ., 166 pp., Cont.-in-part of Appl. No. PCT/US99/21560.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003153752 | A1 | 20030814 | US 2000-537167 | 20000329 |
| US 6713474 | B2 | 20040330 | | |
| WO 2000017203 | A1 | 20000330 | WO 1999-US21560 | 19990917 |

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RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|
| ZA 2001002204 | A | 20020318 | ZA 2001-2204 | 20010316 |
| PRIORITY APPLN. INFO.: | | | US 1998-100832P | P 19980918 |
| | | | US 1998-100833P | P 19980918 |
| | | | US 1998-100834P | P 19980918 |
| | | | US 1998-100946P | P 19980918 |
| | | | WO 1999-US21560 | A2 19990917 |

OTHER SOURCE(S): MARPAT 139:180075
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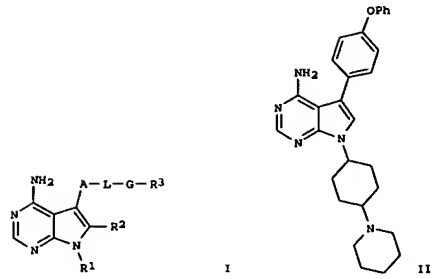
L13 ANSWER 3 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)




AB The title compds. I [A = (un)substituted 6-membered aromatic ring, 5-6 membered heteroarom. ring; L = O, S, SO, SO2, etc.; G = a direct bond, (CH2)j (wherein j = 1-6), alkenylene, cycloalkylene, oxaalkylene; R1 = alkyl, cycloalkyl, bicycloalkyl, etc.; R2 = H, alkyl, cycloalkyl, halo, etc.; R3 = alkyl, alkenyl, cycloalkyl, etc.] and physiol. acceptable salts and metabolites thereof, are inhibitors of serine/threonine and tyrosine kinase activity. Several of the kinases, whose activity is inhibited by compds. I, are involved in immunol., hyperproliferative, or angiogenic processes. Thus, the compds. I can ameliorate disease states where angiogenesis or endothelial cell hyperproliferation is a factor. These compds. can be used to treat cancer and hyperproliferative disorders, rheumatoid arthritis, disorders of the immune system, transplant rejections and inflammatory disorders. All exemplified compds. I significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at ≤50 μM, and some significantly inhibited cdc2 at ≤50 μM. 546 Example prepns. are included. For example, addition of piperidine to 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexanone in DCE and AcOH, followed by treatment with Na[(AcO)3BH], workup and chromatog., gave cis- and trans-II.

L13 ANSWER 4 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 138:32590 CA
TITLE: STI571 (glivec): A new paradigm for the development of innovative therapies in onco-hematology?
AUTHOR(S): Gambacorti, Carlo
CORPORATE SOURCE: Department of Experimental Oncology, National Cancer Institute, Milan, 20133, Italy
SOURCE: Tumori (2001), 87(6), S10-S12
CODEN: TUMOAB; ISSN: 0300-8916
PUBLISHER: Il Pensiero Scientifico Editore
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. STI571 is a rationally developed, potent, and selective inhibitor for abl tyrosine kinases, including Bcr-Abl, as well as c-kit and the platelet-derived growth factor receptor tyrosine kinases. STI571 has been selected as an inhibitor of Bcr/Abl, an oncogenic fusion protein known to cause chronic myelogenous leukemia (CML). CML is a clonal hematopoietic stem cell disorder with an incidence of one to two cases per 100,000 per yr. It progresses through distinct phases: the stable or chronic phase, the accelerated phase, and the blast crisis. The chronic phase is characterized by massive expansion of myeloid cells, which maintain normal maturation. In the later phases, leukemic cells lose their capacity to terminally differentiate, due to addnl. genetic lesions. The result is an acute leukemia, which is highly refractory to therapy.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 138:11038 CA
TITLE: New molecular targets and biological therapies in sarcomas
AUTHOR(S): Scappaticci, F. A.; Marina, N.
CORPORATE SOURCE: Department of Pathology, Stanford University Medical Center, Stanford, CA, 94305, USA
SOURCE: Cancer Treatment Reviews (2001), 27(6), 317-326
CODEN: CTREDJ; ISSN: 0305-7372
PUBLISHER: W. B. Saunders
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The treatment of patients with soft tissue and bone sarcomas has dramatically improved over the last decade. This improvement has been brought about through advances in diagnosis, surgical techniques, conformal radiotherapy, and combination chemotherapy. Further advances in the management of the diverse spectrum of sarcoma patients will reflect tailoring of therapy based on mol. abnormalities. The role of cytogenetics and mol. anal. of fusion or mutated genes in diagnosis, prognosis, and design of biol. treatments is discussed. An example of this approach has been the recent success in treatment of patients with gastrointestinal stromal tumors expressing mutant c-kit with a specific tyrosine kinase inhibitor, STI571. Mol. rearrangements may also serve as targets for designing specific immunotherapies with the fusion gene product. The use of biol. therapies with signal transduction inhibitors, angiogenesis inhibitors, matrix metalloproteinase inhibitors, immunotherapy, differentiation inducers, and gene therapy could complement existing treatments for long-term control of disease. As these newer biol. agents take form, clin. trial design will undergo change to reflect the chronic nature of these therapies.
REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 138:4517 CA
TITLE: Preparation of 3-heteroarylmethylidene-2-indolinone protein kinase inhibitors for use against cancer and other disorders
INVENTOR(S): McMahon, Gerald; Tang, Peng Cho; Sun, Li
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 64 pp., Cont.-in-part of U.S. Ser. No. 74,621.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 6486185 | B1 | 20021126 | US 1998-191458 | | 19981112 |
| US 6316429 | B1 | 20011113 | US 1998-74621 | | 19980507 |
| <-- | | | | | |
| US 2002156083 | A1 | 20021024 | US 2001-819698 | | 20010329 |
| US 6683082 | B2 | 20040127 | | | |
| US 2004106630 | A1 | 20040603 | US 2003-725079 | | 20031202 |
| US 2004106618 | A1 | 20040603 | US 2003-725267 | | 20031202 |

PRIORITY APPLN. INFO.: US 1997-45838P P 19970507
US 1997-59677P P 19970919
US 1998-74621 A2 19980507
US 2001-819698 A3 20010329

OTHER SOURCE(S): MARPAT 138:4517
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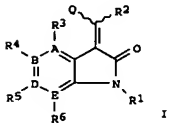
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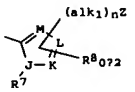
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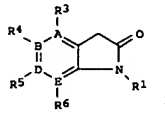
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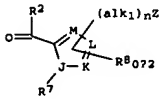
IV

L13 ANSWER 6 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)
AB The present invention relates to novel 3-heteroarylidene-2-indolinone compds. (shown as I; e.g. 3-[3-(2-carboxyethyl)-4-methylpyrrol-2-methylidene]-2-indolinone) and physiol. acceptable salts thereof which modulate the activity of protein kinases and therefore are expected to be useful in the prevention and treatment of protein kinase related cellular disorders such as cancer. In I: A, B, D and E = C and N, it being understood that the N-containing 9-member bicyclic ring formed is one known in the chemical arts; it being further understood that when A, B, D, or E is N, R3, R4, R5 or R6, resp., does not exist. R1 = H, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, carboxy, C-amido and sulfonyl; R2 = H, alkyl, cycloalkyl, aryl, heteroaryl, and heteroalicyclic; R3, R4, R5 and R6 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, -SH, -S-alkyl, -S-cycloalkyl, -S-aryl, -S-heteroaryl, sulfinyl, sulfonyl, sulfonamido, carbonyl, carboxy, cyano, nitro, halo, -OC(O)NR10R11, N-carbamyl, -OC(S)NR10R11, N-thiocarbamyl, C-amido, N-amido, amino and -NR10R11; R10 and R11 = H, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one N; R3 and R4, R4 and R5, or R4 and R5 may combine to form a six-member aryl or heteroaryl ring. Q is a heteroaryl group II in which J = O, N and S; K, L and M = C, N, O and S such that the five-member heteroaryl ring formed is one known in the chemical arts, it being understood that when K, L and M are N, S or O, R8 or -(alk1)nZ cannot be covalently bonded to that atom; when J is N, R7 = H, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, carboxy, C-amido, guanyl and sulfonyl and when J is O or S, R7 does not exist and there is no bond; R8 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, -SH, -S-alkyl, -S-cycloalkyl, -S-aryl, -S-heteroaryl, sulfinyl, sulfonyl, sulfonamido, carbonyl, carboxy, cyano, nitro, halo, -OC(O)NR10R11, N-carbamyl, -OC(S)NR10R11, N-thiocarbamyl, C-amido, N-amido, amino, -NR10R11, trihalomethyl, a five member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring fused to two adjacent atoms of the Q ring; and a six-member cycloalkyl, aryl, heteroaryl, or heteroalicyclic ring fused to two adjacent atoms of the Q ring. R10and R11 = H, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one N; alk1 = optionally substituted methylene (-CRR'-), optionally substituted ethylene (-C(R):C(R')-) and acetylene (-C.tplbond.C-); R and R' = H, alkyl, cycloalkyl, aryl, alkoxy, -S-alkyl, -S-cycloalkyl, aryloxy and halo. N is 0 to 10, inclusive with the proviso that when n is 0, R7 is not alkyl substituted with aryl; and Z is a polar group hydroxy, alkoxy, carboxy, nitro, cyano, carbamyl, amino, quaternary ammonium, amido, ureido, sulfonamido, sulfinyl, sulfonyl, phosphono, phosphonyl, morpholino, piperazinyl and tetrazolo. Also claimed are a combinatorial library of ≥13 I and a method for

L13 ANSWER 6 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)
synthesizing I comprising the step of reacting III with a 2nd reactant IV in a solvent and in the presence of a base at elevated temps. The IC50 results for 12 I for PDGFR, FLK-1R, EGFR, HER2 and IGF-1R protein tyrosine kinases (PTKs) are presented; IC50 refers to that amt. of the tested compd. needed to effect a 50% inhibition of PTK activity in the test indicated with respect to a control in which no compd. of this invention is present. Thus, 3-(2,4-dimethyl-3-ethoxycarbonylpyrrol-5-methylidenyl)-2-indolinone inhibited FLK-1R kinase with IC50 = 0.07 μM.
REFERENCE COUNT: 211 THERE ARE 211 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:383719 CA
TITLE: Regulation of mast cell differentiation
AUTHOR(S): Kitamura, Yukihiko; Morii, Eiichi; Ogihara, Hideki; Jippo, Tomoko; Ito, Akihiko
CORPORATE SOURCE: Department of Pathology, Osaka University Medical School, Suita, Osaka, 565-0871, Japan
SOURCE: International Congress Series (2001), 1224(Histamine Research in the New Millennium), 3-8
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We used various mouse mutants for studying regulation of mast cell differentiation. Their bone marrow origin was shown using giant granules of beige mice as a marker. We found the mast cell deficiency of W/Wv and Sl/Sld mice. The W locus encodes the c-kit receptor tyrosine kinase, and the Sl locus a ligand of c-kit that is the most important growth factor for development of mast cell, atem cell factor. The mi locus encodes a member of the basic helix-lop-helix-leucine zipper protein family of tranacription factor (MITF), and mast cells of mi/mi mice showed various phenotypic abnormalities. Mast cells of mi/mi mice synthesized the mutant mi-MITF in normal amount, and the mi-MITF showed inhibitory effect on the transcription of various mast cell-specific genes. On the other hand, mice of tg/tg possess the transgene insertional mutation at the 5' flanking region of the mi gene and do not express any MITFs. The comparison between phenotypes of mi/mi mast cells and those of tg/tg mast cells gave some insights on the regulation of mast cell phenotypes by transcription factors.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:346843 CA
TITLE: Effects of vascular endothelial and platelet-derived growth factor receptor inhibitors on long-term cultures from normal human bone marrow
AUTHOR(S): Duhrsen, Ulrich; Martinez, Tanja; Vohwinkel, Gabi; Ergun, Suleyman; Sun, Li; McMahon, Gerald; Durig, Jan; Hossfeld, Dieter Kurt; Fiedler, Walter
CORPORATE SOURCE: Zentrum fur Innere Medizin, Abteilung fur Hamatologie, Universitatsklinikum Essen, Germany
SOURCE: Growth Factors (2001), 19(1), 1-17
CODEN: GRFAEC; ISSN: 0897-7194
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Endothelial cells and fibroblasts are important constituents of the hemopoietic microenvironment. Growth and function of these cells are controlled by a variety of cytokines, including VEGF and PDGF. The authors analyzed the effects of novel tyrosine kinase inhibitors targeting the VEGF and PDGF receptors (compds. SU5614 and SU5768) on the performance of long-term cultures from normal human bone marrow. In developing cultures, the inhibitors induced a dose-dependent reduction in stromal fibroblasts, macrophages and endothelial cells with a concomitant decrease in blood cell production and an increase in fat cells. For SU5614, the concentration inhibiting stroma formation by 50% (IC50) was 123 nM, and the IC50 for hemopoietic colony forming cell output was 186 nM. For SU5768, the resp. values were 871 nM and 331 nM. Changes in stroma composition and inhibition of hemopoietic cell production were also demonstrable after delayed addition of the inhibitors to established cultures. By contrast, hemopoietic colony formation in clonogenic agar cultures was unimpaired (IC50 not reached at 100 μM). Immunofluorescence studies and time course analyses suggested that the primary effect of the inhibitors was interference with the proliferation and function of fibroblasts and endothelial cells which in turn resulted in decreased hemopoiesis and increased adipogenesis. This was associated with decreased levels in conditioned media of granulocyte-macrophage colony-stimulating factor, interleukin-6 and leptin. VEGF and PDGF may play a hitherto underestimated role in the control of blood cell formation. VEGF/PDGF receptor inhibitors may have therapeutic potential in stroma diseases such as myelofibrosis. Since they weaken the stimulatory signals provided by the microenvironment, they may also be of value in the treatment of leukemia and other neoplastic bone marrow diseases.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:210939 CA
TITLE: Methods of use of compounds which inhibit the stem cell factor signaling pathway
INVENTOR(S): Longley, B. Jack
PATENT ASSIGNEE(S): The Trustees of Columbia University In the City of New York, USA
SOURCE: U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. Ser. No. 306,143.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2002123031 | A1 | 20020905 | US 1999-474478 | 19991229 |
| US 6989248 | B2 | 20060124 | | |
| US 6576812 | B1 | 20030610 | US 1999-306143 | 19990506 |
| WO 2000067794 | A1 | 20001116 | WO 2000-US12405 | 20000505 |

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|---|---|---|---|---|
| US 6977159 | B1 | 20051220 | US 2002-980572 | 20020923 |

PRIORITY APPLN. INFO.:
US 1999-306143 A2 19990506
US 1999-474478 A2 19991229
WO 2000-US12405 W 20000505

AB The invention provides a method of preventing or treating in a subject contact dermatitis which comprises administering to the subject an amount of a compound capable of inhibiting the stem cell factor signaling pathway effective to prevent or treat contact dermatitis so as to thereby prevent or treat contact dermatitis in the subject. The invention also provides a methods of preventing or treating in a subject hyperpigmentation, asthma, cutaneous inflammation, anaphylaxis and bronchospasm, mastocytosis, tumors which express activated kit, and conception.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:89413 CA
TITLE: Detection of variations in the DNA methylation profile of genes in the determining the risk of disease
INVENTOR(S): Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander
PATENT ASSIGNEE(S): Epigenomics A.-G., Germany
SOURCE: PCT Int. Appl., 636 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 69
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001077373 | A2 | 20011018 | WO 2001-XB1486 | 20010406 |

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG

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| DE 10019058 | A1 | 20011220 | DE 2000-10019058 | 20000406 |

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| AU 2001077487 | A5 | 20011023 | AU 2001-77487 | 20010406 |

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| US 2004067491 | A1 | 20040408 | US 2003-240454 | 20030311 |
| AU 2003204553 | A1 | 20040108 | AU 2003-204553 | 20030605 |
| JP 2004008217 | A2 | 20040115 | JP 2003-160375 | 20030605 |
| US 2004023379 | A1 | 20040205 | US 2003-455212 | 20030605 |

PRIORITY APPLN. INFO.:
DE 2000-10019058 A 20000406
WO 2001-DE1486 W 20010406
DE 2000-10019173 A 20000407
DE 2000-10032529 A 20000630
DE 2000-10043826 A 20000901
WO 2001-EP4016 W 20010406

L13 ANSWER 10 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)

EP 2002-90203 A 20020605

AB The invention relates to an oligonucleotide kit as probe for the detection of relevant variations in the DNA methylation of a target group of genes. The invention further relates to the use of the same for determining the gene variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for determining the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such diseases may be: undesired pharmaceutical side-effects; cancerous diseases; CNS dysfunctions, injuries or diseases; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic disorders and personality disorders; dementia and/or associated syndromes; cardiovascular disease, dysfunction and damage; dysfunction, damage or disease of the gastrointestinal tract; dysfunction, damage or disease of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or disease of the body as an abnormal development process; dysfunction, damage or disease of the skin, muscle, connective tissue or bones; endocrine and metabolic dysfunction, damage or disease; headaches or sexual dysfunction.
This abstract record is one of several records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.

L13 ANSWER 11 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:89412 CA
TITLE: Detection of variations in the DNA methylation profile
of genes in the determining the risk of disease
INVENTOR(S): Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander
PATENT ASSIGNEE(S): Epigenomics A.-G., Germany
SOURCE: PCT Int. Appl., 636 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 69
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001077373 | A2 | 20011018 | WO 2001-XA1486 | 20010406 |
| <-- | | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10019058 | A1 | 20011220 | DE 2000-10019058 | 20000406 |
| <-- | | | | |
| WO 2001077373 | A2 | 20011018 | WO 2001-DE1486 | 20010406 |
| <-- | | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2001077487 | A5 | 20011023 | AU 2001-77487 | 20010406 |
| <-- | | | | |
| EP 1360319 | A2 | 20031112 | EP 2001-955278 | 20010406 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2004067491 | A1 | 20040408 | US 2003-240454 | 20030311 |
| AU 2003204553 | A1 | 20040108 | AU 2003-204553 | 20030605 |
| JP 2004008217 | A2 | 20040115 | JP 2003-160375 | 20030605 |
| US 2004023279 | A1 | 20040205 | US 2003-455212 | 20030605 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| DE 2000-10019058 | A | 20000406 |
| WO 2001-DE1486 | W | 20010406 |
| DE 2000-10019173 | A | 20000407 |
| DE 2000-10032529 | A | 20000630 |

L13 ANSWER 11 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)

| | | |
|---|---|---|
| DE 2000-10043826 | A | 20000901 |
| WO 2001-EP4016 | W | 20010406 |
| EP 2002-90203 | A | 20020605 |

AB The invention relates to an oligonucleotide kit as probe for the detection
of relevant variations in the DNA methylation of a target group of genes. The invention further relates to the use of the same for determining the gene
variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for determining the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such diseases may be: undesired pharmaceutical side-effects; cancerous diseases; CNS dysfunctions, injuries or diseases; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic disorders and personality disorders; dementia and/or associated syndromes; cardiovascular disease, dysfunction and damage; dysfunction, damage or disease of the gastrointestinal tract; dysfunction,
damage or disease of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or disease of the body as an abnormal development process; dysfunction, damage or disease of the skin, muscle, connective tissue or bones; endocrine and metabolic dysfunction, damage or disease; headaches or sexual dysfunction.
This abstract record is one of several records for this document necessitated by the large number of index entries required to fully index the
document and publication system constraints.

L13 ANSWER 12 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:72684 CA
TITLE: Safety and efficacy of imatinib (STI571) in metastatic
gastrointestinal stromal tumors: a phase I study
AUTHOR(S): van Oosterom, Allan T.; Judson, Ian; Verweij, Jaap; Stroobants, Sigrid; Donato di Paola, Eugenio; Dimitrijevic, Sasa; Martens, Marc; Webb, Andrew; Sciot, Raf; Van Glabbeke, Martine; Silberman, Sandra; Nielsen, Ole S.
CORPORATE SOURCE: European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, Department of Oncology, Nuclear Medicine and Pathology, UZ Gasthuisberg, Catholic University, Louvain, B-3000, Belg.
SOURCE: Lancet (2001), 358(9291), 1421-1423
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Lancet Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Gastrointestinal stromal tumors (GISTs) are rare tumors of the gastrointestinal tract characterized by cell-surface expression of the tyrosine kinase KIT (CD117). No effective systemic treatment is available. Imatinib (STI571) inhibits a similar tyrosine kinase, BCR-ABL, leading to responses in chronic myeloid leukemia, and has also been shown to inhibit KIT. The authors did a phase I study to identify the dose-limiting toxic effects of imatinib in patients with advanced soft tissue sarcomas including GISTs. 40 Patients (of whom 36 had GISTs) received imatinib at doses of 400 mg once daily, 300 mg twice daily, 400 mg twice daily, or 500
mg twice daily. Toxic effects and hematol., biochem., and radiol. measurements were assessed during 8 wk of follow-up. 18Fluorodeoxy-glucose
positron-emission tomog. (PET) was used for response assessment in one center. Five patients on 500 mg imatinib twice daily had dose-limiting toxic effects (severe nausea, vomiting, edema, or rash). Inhibition of tumor growth was seen in all but four patients with GISTs, resulting in 19 confirmed partial responses and six as yet unconfirmed partial responses or more than 20% regressions. 24 Of 27 clin. symptomatic patients showed improvement, and 29 of 36 were still on treatment after more than 9 mo. PET scan responses predicted subsequent computed tomog. responses. Imatinib at a dose of 400 mg twice daily is well tolerated during the first 8 wk, side-effects diminish with continuing treatment, and it has significant activity in patients with advanced GISTs. These results provide evidence of a role for KIT in GISTs, and show the potential for the development of anticancer drugs based on specific mol. abnormalities present in cancers.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:61279 CA
TITLE: Role of tyrosine phosphorylation in reactive oxygen species-mediated vascular endothelial cell barrier dysfunction
AUTHOR(S): Zaiman, Ari L.; Dudek, Steven M.; Natarajan, Viswanathan; Garcia, Joe G. N.
CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, 21224, USA
SOURCE: NATO Science Series, Series I: Life and Behavioural Sciences (2001), 336(Etiology and Treatment of Acute Lung Injury), 158-168
CODEN: NSSSC9; ISSN: 1566-7693
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The physiol. effects of reactive oxygen species (ROS) modulation of endothelial cell function through protein tyrosine phosphorylation-dependent signaling modeling systems were studied using hydrogen peroxide and diperoxovanadate (DPV). DPV stimulated a rapid increase in phosphotyrosine-containing proteins at the cell periphery which correspond
well to the time frame of altered permeability with the distribution suggesting alterations in focal adhesion and adherens junction proteins. DPV treatment resulted in the rapid phosphorylation of p125 FAK and a delayed but significant time dependent phosphorylation of cadherins and β-catenins. DPV resulted in the tyrosine phosphorylation of myosin light chain kinase (MLCK) which was associated with increased MLCK activity
and association with cortactin and pp60src. Specific inhibition of MLCK significantly attenuated DPV mediated permeability, and inhibition of Rho by C3 exotoxin totally abolished DPV effects.
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 14 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:58416 CA
TITLE: Transcription factor BACH2 is transcriptionally regulated by the BCR/ABL oncogene
AUTHOR(S): Vieira, Sara A. D.; Deininger, Michael W. N.; Sorour, Amani; Sinclair, Paul; Foroni, Letizia; Goldman, John M.; Melo, Junia V.
CORPORATE SOURCE: Department of Haematology, Imperial College School of Medicine, Hammersmith Hospital, London, W12 0NN, UK
SOURCE: Genes, Chromosomes & Cancer (2001), 32(4), 353-363
CODEN: GCCAES; ISSN: 1045-2257
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Expression of BCR/ABL, a constitutively active tyrosine kinase, is a primary event in the pathogenesis of chronic myeloid leukemia (CML) and Ph-pos. acute lymphoblastic leukemia (Ph+ALL). Inhibition of the BCR/ABL kinase activity in the BV173 CML cell line with STI571 resulted in a significant overexpression of a 10-kb novel mRNA, found to be the human ortholog of the murine Bach2, a B-cell-specific transcription factor. The human BACH2 cDNA is >9,120 bp long and includes an open reading frame of 2,526 bp encoding a protein with a basic leucine zipper (bZip) and a BTB/POZ domain, mediating DNA-binding and heterodimerization. BACH2 was consistently upregulated (2-10-fold) in all 10 Ph+ lymphoid lines tested following BCR/ABL inhibition. In CML myelod cell lines (n = 8) and BCR/ABL-neg. lines (n = 6), BACH2 was either undetectable by Northern blotting or did not change in response to STI571, suggesting that BACH2 repression by BCR/ABL may be specifically relevant to lymphoid transformation. Quant. RT/PCR revealed a significantly lower level of BACH2 expression in leukocytes from patients with CML (n = 24) as compared to normal individuals (n = 23) (P < 0.0005). Moreover, CD34+ cells treated in vitro with STI571 exhibited a consistent upregulation of BACH2 in 8 of 10 CMLs but in none of the 9 normal individuals tested. Transcription regulation of BACH2 in BCR/ABL-pos. cells was exerted via the MEK pathway, as shown by their responses to the U0126-specific inhibitor. Radiation hybrid mapping and FISH revealed that BACH2 is located on chromosome 6, band q15, a region frequently associated with deletions in ALL and non-Hodgkin's lymphoma, suggesting its possible role as a tumor suppressor gene. However, no rearrangement or loss of signal was observed by Southern blotting in 34 lymphomas, 10 B-cell ALLs, or seven reactive lymph nodes. The pattern of BACH2 expression in BCR/ABL-pos. cells suggests that transcriptional repression by this regulator is impaired in CML and may contribute to the emergence of lymphoid blast crisis.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 15 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:56717 CA
TITLE: Molecular therapy for multiple myeloma
AUTHOR(S): Martinelli, Giovanni; Tosi, Patrizia; Ottaviani, Emanuela; Soverini, Simona; Tura, Sante
CORPORATE SOURCE: Institute of Hematology and Medical Oncology Seragnoli, University of Bologna, Bologna, 40138, Italy
SOURCE: Haematologica (2001), 86(9), 908-917
CODEN: HAEMAX; ISSN: 0390-6078
PUBLISHER: Ferrata Storti Foundation
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Background and Objectives. Several mol. and cytogenetic advances have suggested novel therapeutic strategies that could help reach an eventual cure for multiple myeloma (MM). Evidence and Information Sources. Identification of novel, MM-specific mol. targets should pave the way for drugs that can specifically attack the neoplastic cells while sparing the normal ones. Drugs that alter the marrow microenvironment - such as bisphosphonates, proteasome inhibitors (e.g. PS-341/LDP341), lactacystin or LLNV compds. - induce apoptosis or G1 growth arrest and alter the adhesion of MM cells to marrow stroma. These drugs that modify the microenvironment have a more solid scientific basis and may, therefore, have more realistic implicstions in MM treatment. Of these, novel vascular endothelial growth factor (VEGF) inhibitors , such as SU5416 and SU6668, block tumor-cell adhesion and could disrupt MM cell proliferation. Similarly, tyrosine kinase inhibitors (TKI) such as fibroblast growth factor receptor (FGFR) inhibitors, may serve when the FGFR3 gene is overexpressed due to the t(4;14)(p16.3;q32) and/or is activated by point mutations. In cases carrying the translocation and expressing the IgH/WHSC1-MMSET hybrid transcripts, histone deacetylase (HDAC) inhibitors could be useful, but their possible clin. use needs to be supported by more biol. studies. Tumor necrosis factor α-related apoptosis-inducing ligand (TRAIL) induces apoptosis in MM cell lines and primary cells. The proliferative signaling pathway of FGFR3 is medisted by Ras (Ras-activating mutations are frequently found in MM), which presents a possible target for farnesyltransferase inhibitors (used alone or in association with IFN-α). Perspectives. In several of these options, preclin. studies have proved encouraging, and clin. trials are now getting underway.
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:18476 CA
TITLE: Hepatic stellate cell proliferation is an early platelet-derived growth factor-mediated cellular event in rat cholestatic liver injury
AUTHOR(S): Kinnman, Nils; Goria, Odile; Wendum, Dominique; Gendron, Marie-Claude; Rey, Colette; Poupon, Raoul; Housset, Chantal
CORPORATE SOURCE: Service d'Hepato-Gastroenterologie, Institut National de la Sante et de la Recherche Medicale U402, Paris, Fr.
SOURCE: Laboratory Investigation (2001), 81(12), 1709-1716
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB After liver injury, hepatic stellate cells (HSC) undergo a pleiotropic response termed "activation" that also occurs in culture models and ultimately leads to the conversion of HSC into myofibroblasts expressing smooth muscle -actin (-SMA). The onset of HSC proliferation in primary culture coincides with the induction of platelet-derived growth factor receptor- (PDGFR-) expression, while platelet-derived growth factor (PDGF) is the most potent mitogen for culture-activated HSC. Yet, the mechanisms and the stage of activation required for HSC proliferation in the intact liver are still uncertain. In the present study, we analyzed the proliferative response of HSC to rat cholestatic liver injury and the role of PDGF in this response. After in vivo incorporation of bromodeoxyuridine (BrdU), pure vitamin A-containing HSC were isolated at different time points after bile duct ligation (BDL) or sham operation and were analyzed by means of flow cytometry. The induction of HSC proliferation, as ascertained by BrdU incorporation, occurred between 24 and 48 h and reached a plateau as soon as 48 h after BDL. Flow cytometry and immunoblot analyses of HSC indicated that the induction of proliferation in HSC coincided with the up-regulation of PDGFR-protein on their surface but preceded that of -SMA. A dose-dependent inhibition of PDGF-BB-induced HSC proliferation by STI 571, a PDGF receptor tyrosine kinase inhibitor, was documented in vitro. Daily i.p. injections of STI571 (20 mg/kg) caused a 60% reduction in BrdU pos. isolated HSC and in the amount of desmin-immunoreactive sinusoidal cells on liver tissue sections in 48-h bile duct-ligated rats. These results indicate that cholestatic liver injury elicits an early proliferative response in HSC that is mainly mediated by PDGF, and which precedes HSC phenotypic conversion into myofibroblasts.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 17 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 137:15067 CA
TITLE: Tyrosine kinase inhibitors : From rational design to clinical trials
AUTHOR(S): Traxler, Peter; Bold, Guido; Buchdunger, Elisabeth; Caravatti, Giorgio; Furet, Pascal; Manley, Paul; O'Reilly, Terence; Wood, Jeanette; Zimmermann, Juerg
CORPORATE SOURCE: Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: Medicinal Research Reviews (2001), 21(6), 499-512
CODEN: MRREDD; ISSN: 0198-6325
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Protein kinases play a crucial role in signal transduction as well as in cellular proliferation, differentiation, and various regulatory mechanisms. The inhibition of growth related kinases, especially Tyr kinases, might provide new therapies for diseases such as cancer. The progress made in the crystallization of protein kinases has confirmed that the ATP-binding domain of Tyr kinases is an attractive target for drug design. Three successful examples of drug design at Novartis using a Tyr kinase as a mol. target are described. PK1166, a pyrrolo[2,3,-d]pyrimidine derivative, is a dual inhibitor of both the EGFR and the ErbB2 kinases. The compound entered clin. trials in 1999, based on its favorable pre-clin. profile: potent inhibition of EGF-mediated signalling in cells, in vivo antitumor activity in several EGFR over-expressing xenograft tumor models in nude mice, long-lasting inhibition of EGF-stimulated EGFR auto-phosphorylation in tumor tissue, good oral bioavailability in animals, and no prohibitive in vitro and in vivo toxicity findings. The anilino-phthalazine derivative PTK787/ZK222584 (Phase I, co-developed by Schering AG, Berlin) is a potent and selective inhibitor of both the KDR and Flt-1 kinases with interesting anti-angiogenic and pharmacokinetic properties (orally bioavailable). STI 571 (Glivec, Gleevec), a phenylamino-pyrimidine derivative, is a potent inhibitor of the Abl Tyr kinase, which is present in 95% of patients with chronic myelogenous leukemia (CML). The compound specifically inhibits proliferation of v-Abl and Bcr-Abl expressing cells (including cells from CML patients) and shows anti-tumor activity as a single agent in animal models at well-tolerated doses. Pharmacol. relevant concns. are achieved in the plasma of animals (oral administration). Promising data from phase I and II clin. trials in CML patients (98% hematol. response rate in Phase I) support the fact that the STI571 represents a new treatment modality for CML. In addition, potent inhibition of the PDGFR and c-Kit Tyr kinases also indicates its possible clin. use in solid tumors.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 18 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:366819 CA
TITLE: Role of Src Kinase in Diperoxovanadate-Mediated Activation of Phospholipase D in Endothelial Cells
AUTHOR(S): Parinandi, Narasimham L.; Roy, Shukla; Shi, Shu; Cummings, Rhett J.; Morris, Andrew J.; Garcia, Joe G. N.; Natarajan, Viswanathan
CORPORATE SOURCE: Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, 21224, USA
SOURCE: Archives of Biochemistry and Biophysics (2001), 396(2), 231-243
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have shown earlier that oxidant-induced activation of phospholipase D (PLD) in vascular endothelial cells (ECs) is regulated by protein tyrosine kinases. To further understand the regulation of oxidant-induced PLD activation, we investigated the role of Src kinase. Treatment of bovine pulmonary artery ECs (BPAECs) with a model oxidant, diperoxovanadate (DPV), at 5 μM concentration, for 30 min, stimulated PLD activity (four- to eightfold), which was attenuated by tyrosine kinase inhibitors and by Src kinase-specific inhibitors PP-1 and PP-2, in a dose- and time-dependent fashion. Furthermore, BPAECs exposed to DPV (5 μM) for 2 min showed activation of Src kinase as observed by increased tyrosine phosphorylation and autophosphorylation in Src immunoppts., which was attenuated by PP-2. Src immunoppts. of cell lysates from control BPAECs exhibited PLD activity in cell-free prepns., which was Arf- and Rho-sensitive and was enhanced at 2 min of DPV (5 μM) treatment. Also, Western blots of Src immunoppts. of control cells revealed the presence of PLD1 and PLD2, suggesting the association of PLD with Src kinase under basal conditions. However, exposure of cells to DPV (5 μM) for 2 min enhanced the association of PLD2 but not PLD1 with Src. Western blotting of immunoppts. of PLD1 and PLD2 isoforms of control BPAECs revealed the presence of Src under basal conditions and exposure of cells to DPV (5 μM) for 2 min enhanced the association of PLD2 with Src in PLD2 immunoppts. Transient expression of a dominant neg. mutant of Src in BPAECs attenuated DPV- but not TPA-induced PLD activation. In cell-free prepns., Src did not phosphorylate either PLD1 or PLD2 compared to protein kinase Cα or p38 mitogen-activated protein kinase. These data show for the first time a direct association of Src with PLD in ECs and regulation of PLD in intact cells. (c) 2001 Academic Press.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 19 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:339493 CA
TITLE: Modified antibodies agonistic to apoptosis-signal transduction useful for treating cancer, inflammation, dysendocrinism and blood diseases
INVENTOR(S): Fukushima, Naoshi; Tsuchiya, Masayuki; Uno, Shinsuke; Ohtomo, Toshihiko; Yabuta, Naohiro; Tsunoda, Hiroyuki
PATENT ASSIGNEE(S): Chugai Seiyaku Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 218 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002033073 | A1 | 20020425 | WO 2001-JP9260 | 20011022 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| WO 2001066737 <-- | A1 | 20010913 | WO 2001-JP1912 | 20010312 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| WO 2001079494 <-- | A1 | 20011025 | WO 2001-JP3288 | 20010417 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002010918 | A5 | 20020429 | AU 2002-10918 | 20011022 |
| CA 2424371 | AA | 20030401 | CA 2001-2424371 | 20011022 |
| EP 1327681 | A1 | 20030716 | EP 2001-978852 | 20011022 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2004242847 | A1 | 20041202 | US 2003-399585 | 20030418 |

PRIORITY APPLN. INFO.: JP 2000-321821 A 20001020
JP 2000-321822 A 20001020

L13 ANSWER 18 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)

L13 ANSWER 19 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)

| | | |
|---|---|---|
| WO 2001-JP1912 | W | 20010312 |
| WO 2001-JP3288 | W | 20010417 |
| JP 2001-277314 | A | 20010912 |
| US 2000-523095 | A | 20000310 |
| JP 2000-115246 | A | 20000417 |
| WO 2001-JP9260 | W | 20011022 |

AB Modified antibodies containing at least two H chain V domains and at least two L chain V domains of a monoclonal antibody which transduces a signal into cells by crosslinking a cell surface mol. or intracellular mol. to thereby serve as an agonist. The modified agonistic antibodies are specific to cell surface mol. or intracellular mol. such as hormone receptor, cytokine receptor, tyrosine kinase receptor or nuclear receptor. The agonistic effect is induction of apoptosis, cell proliferation, cell differentiation, mitosis, and/or cell cycle regulation. Because of being usable as a signal transduction agonist, these modified antibodies are useful as preventive and/or remedy etc. for various diseases such as caner, inflammation, dysendocrinism and blood diseases.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 20 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:335579 CA
TITLE: Monoclonal antibody-mediated manipulation as a tool for dissecting genetic pathways underlying specific embryonic processes
AUTHOR(S): Nishikawa, Shin-Ichi; Nishikawa, Satomi
CORPORATE SOURCE: Center for Developmental Biology, Riken, Japan
SOURCE: Pigment Cell Research (2001), 14(4), 249-255
CODEN: PCREEA; ISSN: 0893-5785
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with refs. The technol. to produce monoclonal antibody (mAb) is one of mainstays supporting current biol. Identification and isolation of a specific mol. in situations where many other mols. coexist is the most popular way of using this technol. Some mAb can trigger or suppress the function of a given mol., thus having a potential for use in manipulating developmental processes. A decade ago, we demonstrated that embryonic components of pigment cell development could be manipulated by injection of a mAb that inhibits the function of the c-Kit tyrosine kinase receptor (RTK) into pregnant mice. While we believe that no other methods were available at that time to freely trigger or suppress the function of such mols. as c-Kit, mol. genetic technologies enabling the same task have been developed recently. In this article, we want to give a general overview of our previous experience of using mAb for manipulating embryonic processes, and discuss the potential of this technol. in the age of new mol. genetics.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 21 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:318825 CA
TITLE: Pyrrolo[2,3-d]pyrimidine and pyrazolo[3,4-d]pyrimidine derivatives as selective inhibitors of the EGF receptor tyrosine kinase
AUTHOR(S): Caravatti, G.; Bruggen, J.; Buchdunger, E.; Cozens, R.; Furet, P.; Lydon, N.; O'Reilly, T.; Traxler, P.
CORPORATE SOURCE: TA Oncology, Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: ACS Symposium Series (2001), 796(Anticancer Agents), 231-244
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:318825
AB The EPG receptor tyrosine kinase (EGFR) is an attractive target for the development of agents directed against tumors which either overexpress the EGFR or which have a mutated or amplified gene encoding the EGFR. Several ATP-competitive inhibitors of this kinase have shown promising in vitro and in vivo efficacy and are currently in different stages of clin. development. One of them is PKI166, a pyrrolo[2,3-d]pyrimidine, which has been selected from a large series of pyrrolo[2,3-d]pyrimidines and structurally related pyrazolo[3,4-d]pyrimidines. The discovery and preclin. data of PKI166 are summarized.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 22 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:307630 CA
TITLE: Mildly oxidized LDL induces activation of platelet-derived growth factor β-receptor pathway
AUTHOR(S): Escargueil-Blanc, Isabelle; Salvayre, Robert; Vacaresse, Nathalie; Juergens, Guenther; Darblade, Benoit; Arnal, Jean-Francois; Parthasarathy, Sampath; Negre-Salvayre, Anne
CORPORATE SOURCE: Biochemistry Dep, IFR-31, CHU Rangueil, INSERM U-466, Toulouse, Fr.
SOURCE: Circulation (2001), 104(15), 1814-1821
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background - Mildly oxidized LDL (moxLDL) is thought to play a role in atherogenesis. MoxLDL induces derivatization of cell proteins and triggers a variety of intracellular signaling. We aimed to investigate whether moxLDL-induced protein derivatization may influence the activity of platelet-derived growth factor receptor β ( PDGFR.beta.), a tyrosine kinase receptor of major importance in vascular biol. and atherogenesis. Methods and Results - In cultured rabbit arterial smooth muscle cells, moxLDL induces activation of the PDGFR.beta. signaling pathway, as shown by PDGFR.beta. tyrosine phosphorylation on Western blot and coimmunopptn. of SH2-containing proteins. The cellular events involved in the moxLDL-induced PDGFR.beta. activation can be summarized as follows. Oxidized lipids from moxLDL trigger two phases of PDGFR.beta. activation involving two sep. mechanisms, as shown by expts. on cultured cells (in situ) and on immunopurified PDGFR.beta. (in vitro):(1) the first phase may be mediated by 4-hydroxynonenal, which induces PDGFR β adduct formation and subsequent PDGFR.beta. activation (antioxidant-insensitive step); (2) the second phase involves ceramide-mediated generation of H2O2 (these steps being inhibited by tosylphenylalanylchloromethylketone, an inhibitor of ceramide formation, and by antioxidant BHT, exogenous catalase, or overexpressed human catalase). Because 4-hydroxynonenal-PDGFR.beta. adducts are also detected in atherosclerotic aortas, it is suggested that this novel mechanism of moxLDL-induced PDGFR.beta. activation may occur during atherogenesis. Conclusions - MoxLDL acts as a local autoparacrine mediator in the vascular wall, and PDGFR.beta. acts as a sensor for both oxidized lipids and oxidative stress. This constitutes a novel mechanism of PDGFR.beta. activation in atherosclerotic areas.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 23 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:303452 CA
TITLE: STI571: a new treatment modality for CML?
AUTHOR(S): Zimmermann, Jurg; Furet, Pascal; Buchdunger, Elisabeth
CORPORATE SOURCE: Pharma Research, Novartis, Basel, CH-4002, Switz.
SOURCE: ACS Symposium Series (2001), 796(Anticancer Agents), 245-259, 1 plate
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. STI571 is a protein-tyrosine kinase inhibitor which potently inhibits the Abl tyrosine kinase in vitro and in vivo. The compound specifically inhibits proliferation of v-abl and bcr-abl expressing cells, suggesting that it is not a general antimitotic agent. In addition, STI571 is a potent inhibitor of the platelet-derived growth factor receptor kinase (PDGF-R) and of the receptor kinase for stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated biochem. events. In contrast, it does not affect signal transduction mediated by other stimuli including epidermal growth factor (EGF), insulin and phorbol esters. Pharmacokinetic studies in various animal species demonstrate that pharmacol. relevant concns. are achieved in the plasma following oral administration of the drug. STI571 shows anti-tumor activity as a single agent in animal models at well tolerated doses. Promising data from phase I clin. trials in CML (chronic myeloid leukemia) patients support the notion that STI571 represents a new treatment modality for CML.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 24 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:260989 CA
TITLE: p73 is a growth-regulated protein in vascular smooth muscle cells and is present at high levels in human atherosclerotic plaque
AUTHOR(S): Weiss, R. H.; Howard, L. L.
CORPORATE SOURCE: Department of Internal Medicine, Division of Nephrology, University of California, Davis, CA, 95616, USA
SOURCE: Cellular Signalling (2001), 13(10), 727-733
CODEN: CESIEY; ISSN: 0898-6568
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB P73 is a newly described homolog of the tumor suppressor p53 that was cloned serendipitously and subsequently shown to possess considerable homol. in the most evolutionarily conserved p53 domains. Yet despite the fact that p53 and p73 have extensive structural similarities, their functions are proving to be quite different. We now show that p73 is a growth-regulated protein in the vasculature, being markedly increased in cultured vascular smooth muscle (VSM) cells stimulated with 10% serum, with no significant change in p73 mRNA levels. Stability of p73 is increased after serum stimulation and, probably contributing to this increase in p73 stability, the c-Abl oncogene protein displays a higher mol. weight species and is probably phosphorylated and activated in serum-stimulated VSM cells. The serum-medisted induction of p73 is not altered when the cells are incubated with inhibitors of the MAP/ERK pathway or tyrosine kinases, and is not stimulated by PDGF-BB, demonstrating that the mechanism of the increase in p73 does not involve this classical receptor tyrosine kinase growth factor signaling cascade. P73 is markedly increased in plaque tissue taken from atherosclerotic human carotid arteries, but not in comparable intimal scrapings from normal human arteries. Our data indicate that the tumor suppressor homolog p73 probably plays a role in VSM cell cycle progression, being mediated by a specific, as yet unidentified, serum component, and identifies a new function for this protein as being important in the pathogenesis of human atherosclerosis as well as other vascular diseases.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 25 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:214546 CA
TITLE: Gastrointestinal stromal tumors with KIT mutations exhibit a remarkably homogeneous gene expression profile
AUTHOR(S): Allander, Susanne V.; Nupponen, Nina N.; Ringner, Markus; Hostetter, Galen; Maher, Greg W.; Goldberger, Natalie; Chen, Yidong; Carpten, John; Elkahloun, Abdel G.; Meltzer, Paul S.
CORPORATE SOURCE: Cancer Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD, 20892, USA
SOURCE: Cancer Research (2001), 61(24), 8624-8628
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Gastrointestinal stromal tumors (GISTs), the most common mesenchymal tumors of the digestive tract, are believed to arise from the interstitial cells of Cajal. GISTs are characterized by mutations in the proto-oncogene KIT that lead to constitutive activation of its tyrosine kinase activity. The tyrosine kinase inhibitor STI 571, active against the BCR-ABL fusion protein in chronic myeloid leukemia, was recently shown to be highly effective in GISTs. We used 13,826-element cDNA microarrays to define the expression patterns of 13 KIT mutation-pos. GISTs and compared them with the expression profiles of a group of spindle cell tumors from locations outside the gastrointestinal tract. Our results showed a remarkably distinct and uniform expression profile for all of the GISTs. In particular, hierarchical clustering of a subset of 113 cDNAs placed all of the GIST samples into one branch, with a Pearson correlation >0.91. This homogeneity suggests that the mol. pathogenesis of a GIST results from expansion of a clone that has acquired an activating mutation in KIT without the extreme genetic instability found in the common epithelial cancers. The results provide insight into the histogenesis of GIST and the clin. behavior of this therapeutically responsive tumor.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 26 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:197534 CA
TITLE: Establishment and characterization of immortalized ovine Sertoli cell lines
AUTHOR(S): Merhi, Raghida Abou; Guillaud, Laurent; Delouis, Claude; Cotinot, Corinne
CORPORATE SOURCE: Unite de Biologie du developpement et Biotechnologies, INRA, Jouy-en-Josas, 78350, Fr.
SOURCE: In Vitro Cellular & Developmental Biology: Animal ( 2001), 37(9), 581-588
CODEN: IVCAED; ISSN: 1071-2690
PUBLISHER: Society for In Vitro Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objective of this study was to generate immortalized Sertoli cell lines from prepubertal lamb testes to facilitate investigations during the course of testicular differentiation. The Sertoli cells were enzymically isolated and immortalized by transfection, with the sequences coding for the SV40 large T-antigen fused downstream of regulatory elements from the human vimentin gene. The different cell lines were pos. stained with antibodies to vimentin and transferrin, in agreement with their Sertoli origin. Reverse transcriptase polymerase chain reaction was used to analyze the specific expression of mol. markers (clusterin/sulfated glycoprotein [SGP-2], FSH [rFSH], α- inhibin, anti-Mullerian hormone, Wilms' tumor gene [WT-1], steroidogenic factor 1 [SF-1], SRY-related HMG box gene g [SOX9], and sex-determining region of Y chromosome) normally expressed in this cellular type. All were shown to express messenger ribonucleic acids (mRNA) for SGP-2, α-inhibin, WT-1, SOX9, and SF-1 (except SF-1 for clone number 1). Moreover, the authors performed alkaline phosphatase and receptor tyrosine kinase p145 (c-kit) detection to ensure the absence of contamination by peritubular, germ cells, and Leydig cells. Both tests were neg. for all the seven cell lines. These ovine Sertoli cell lines are the first ones obtained from livestock that exhibit specific Sertoli cell characteristics resembling different stages of phenotypic development. They provide useful in vitro model systems for toxicol. investigations, coculture, and transfection expts., making it possible to study signal transduction pathways, cell-cell interactions, and gene expression in species other than rodents.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 27 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:193503 CA
TITLE: Tyrosine kinase inhibitor imatinib (STI571) as an anticancer agent for solid tumours
AUTHOR(S): Joensuu, Heikki; Dimitrijevic, Sasa
CORPORATE SOURCE: Department of Oncology and Radiotherapy, Helsinki University Central Hospital, Helsinki, 00029, Finland
SOURCE: Annals of Medicine (Helsinki, Finland) (2001 ), 33(7), 451-455
CODEN: ANMDEU; ISSN: 0785-3890
PUBLISHER: Royal Society of Medicine Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Imatinib mesylate, also known as STI571 or CGP57148, is a competitive inhibitor of a few tyrosine kinases, including BCR-ABL, ABL, KIT, and the platelet-derived growth factor receptors (PDGF-R). It binds to the ATP-binding site of the target kinase and prevents the transfer of phosphate from ATP to the tyrosine residues of various substrates. At oral doses of 300 mg or greater, the vast majority of patients with chronic myeloid leukemia achieve a hematol. response and this is usually associated with limited toxicity. Imatinib also has substantial activity in Philadelphia chromosome-pos. acute lymphoblastic leukemia expressing the BCR-ABL fusion protein. Gastrointestinal stromal tumors (GISTs) have also been evaluated for clin. activity of imatinib. About 90% of malignant GISTs harbor a mutation in c-kit leading to KIT receptor autophosphorylation and ligand-independent activation. According to initial clin. studies, more than 50% of GISTs respond to therapy within a few months, and only about 10-15% progress. The potential for cure and the optimal length of treatment are currently not known. Several other human cancers may over-express KIT or PDGF-R, and clin. trials to evaluate the role of imatinib in the treatment of such cancers are currently ongoing. Imatinib is an example of a specifically designed, highly targeted cancer therapy, which poses novel requirements for both pathol. labs. and clinicians in terms of identifying the major mol. mechanisms involved in tumor growth.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 28 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:181550 CA
TITLE: Mutational analysis of the regulatory function of the c-Abl Src homology 3 domain
AUTHOR(S): Brasher, Bradley B.; Roumiantsev, Sergei; Van Etten, Richard A.
CORPORATE SOURCE: Enanta Pharmaceuticals, Watertown, MA, 02472, USA
SOURCE: Oncogene (2001), 20(53), 7744-7752
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The catalytic activity of the c-Abl tyrosine kinase is tightly regulated by its Src homol. 3 (SH3) domain through a complex mechanism that may involve intramol. binding to Pro242 in the linker region between the SH2 and catalytic domains as well as interactions with a trans-inhibitor. The authors analyzed the effect of mutation or replacement of SH3 on c-Abl tyrosine kinase activity and transformation. Random mutagenesis of SH3 identified several novel point mutations that dysregulated c-Abl kinase activity in vivo, but the RT loop was insensitive to mutational activation. Activating SH3 mutations abolished binding of proline-rich SH3 ligands in vitro, while mutations at Ser140 in the connector between the SH3 and SH2 domains activated Abl kinase activity in vivo and in vitro but did not impair SH3 ligand-binding. Abl was regulated efficiently when its SH3 domain was replaced with a heterologous SH3 from c-Src that binds a different spectrum of proline-rich ligands, but not by substitution of a modular WW domain with similar ligand-binding specificity. These results suggest that the SH3 domain regulates Abl principally by binding to the atypical intramol. ligand Pro242 rather than a canonical PxxP ligand. Coordination between the SH3 and SH2 domains mediated by the connector region may be required for regulation of Abl even in the absence of SH2 ligand binding.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 29 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:180974 CA
TITLE: Choosing between growth arrest and apoptosis through the retinoblastoma tumor suppressor protein, Abl and p73
AUTHOR(S): Wang, J. Y. J.; Ki, S. W.
CORPORATE SOURCE: Division of Biology and the Cancer Center, University of California, San Diego, La Jolla, CA, 92093-0322, USA
SOURCE: Biochemical Society Transactions (2001), 29(6), 666-673
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The choice between growth arrest and apoptosis is made during differentiation, leading to survival with permanent arrest (e.g. neurons), or to death (e.g. epithelium). Genotoxic stress can also cause growth arrest or apoptosis, in addition to the activation of cell cycle checkpoint pathways. The p53 tumor suppressor can simulate growth arrest and apoptosis in response to DNA damage. Thus, p53 alone is not sufficient to specify these two mutually exclusive fates in damaged cells. The retinoblastoma tumor suppressor protein (RB) is a necessary downstream effector in p53-mediated growth arrest. RB inhibits E2F and the nuclear c-Abl tyrosine kinase. Interestingly, E2F activates the transcription of p73 mRNA and c-Abl stabilizes the p73 protein and activates its pro-apoptotic function. Because of RB, the c-Abl/p73 apoptosis pathway is activated in S/G2 cells but not in G1 cells. Taken together, the current data suggests RB to be an important player in directing the choice between permanent arrest and apoptosis. The antagonism between RB and c-Abl/p73 may modulate the function of p53 to direct the choice between growth arrest and apoptosis in DNA damaged cells.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 30 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:129425 CA
TITLE: The sphingosine-1-phosphate receptor EDG-1 is essential for platelet-derived growth factor-induced cell motility
AUTHOR(S): Rosenfeldt, H. M.; Hobson, J. P.; Milstien, S.; Spiegel, S.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Georgetown University Medical Center, Washington, DC, 20007, USA
SOURCE: Biochemical Society Transactions (2001), 29(6), 836-839
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB EDG-1, encoded by the endothelial differentiation gene-1, is a heterotrimeric guanine nucleotide binding protein-coupled receptor (GPCR) for sphingosine-1-phosphate (SPP) that has been shown to stimulate angiogenesis and cell migration in cultured endothelial cells. Unexpectedly, EDG-1 knockout embryos had a normal blood vessel network, vasculogenesis and angiogenesis, but died in utero owing to massive hemorrhaging as a result of failure of smooth muscle cells and pericytes to migrate around the circumference and reinforce endothelial tubes. This vascular maturation defect is similar to the phenotype of mice homozygous for disrupted alleles of platelet-derived growth factor B-subunit homodimer (PDGF-BB) or its receptor PDGFR-β. The authors found that fibroblasts from EDG-1 null embryos did not migrate toward PDGF or SPP, and inhibition of motility correlated with defective activation of the small guanosine triphosphatase Rac, which is required for lamellipodia formation and directional locomotion. Moreover, the authors showed that PDGF-directed cell migration requires both sphingosine kinase activation and expression of EDG-1, suggesting a functional link between PDGF signaling and EDG-1. Indeed, treatment of wild-type cells with PDGF transactivated EDG-1 as determined by translocation of β-arrestin and phosphorylation of EDG-1. These findings reveal a new paradigm for receptor cross-communication in which activation of a GPCR by a receptor tyrosine kinase is critical for cell motility. The authors' observations might also clarify the role of EDG-1 in vascular maturation and angiogenesis.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 31 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:128524 CA
TITLE: Development of ELISA system for screening of specific binding inhibitors for Src homology (SH)2 domain and phosphotyrosine interactions
AUTHOR(S): Lee, Sang Seop; Lee, Kyung Im; Yoo, Jiyun; Jeong, Moon-Jin; Park, Young-Mee; Kwon, Byoung-Mog; Bae, Yun Soo; Han, Mi Young
CORPORATE SOURCE: Laboratory of Cell Biology, Korea Research Institute of Bioscience and Biotechnology, Taejon, 305-600, S. Korea
SOURCE: Journal of Biochemistry and Molecular Biology ( 2001), 34(6), 537-543
CODEN: JBMBE5; ISSN: 1225-8687
PUBLISHER: Springer-Verlag Singapore Pte. Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study, an in vitro ELISA system to assess the interaction between Src homol. (SH)2 domains and phosphotyrosine in peptides was established using purified GST-conjugated SH2 proteins and synthetic biotinylated phosphotyrosine-containing oligopeptides. The SH2 domains bound the relevant phosphopeptides that were immobilized in the streptavidin-coated microtiter plate in a highly specific and dose-dependent manner. The EGF receptor (EGFR)-, T antigen (T Ag)-, and PDGF receptor (PDGFR)-derived phosphopeptides interacted with the growth factor receptor binding protein (Grb)2/SH2, Lck/SH2, and phosphatidylinositol 3-kinase (PI3K) p85/SH2, resp. No cross-reactions were observed Competitive inhibition expts. showed that a short phosphopeptide of only four amino acids was long enough to determine the binding specificity. Optimal concns. of the GST-SH2 fusion protein and phosphopeptide in this new ELISA system for screening the binding blockers were chosen at 2nM and 500nM, resp. When two candidate compds. were tested in the authors' ELISA system, they specifically inhibited the Lck/SH2 and/or p85/SH2 binding to the relevant phosphopeptides. The authors' results indicate that this ELISA system could be used as an easy screening method for the discovery of specific binding blockers of protein-protein interactions via SH2 domains.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 32 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:114676 CA
TITLE: Phosphorylation and structure-based functional studies
reveal a positive and a negative role for the activation loop of the c-Abl tyrosine kinase
AUTHOR(S): Dorey, Karel; Engen, John R.; Kretzschmar, Jana; Wilm, Matthias; Neubauer, Gitte; Schindler, Thomas; Superti-Furga, Giulio
CORPORATE SOURCE: Developmental Biology Programme, European Molecular Biology Laboratory, Heidelberg, 69117, Germany
SOURCE: Oncogene (2001), 20(56), 8075-8084
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB C-Abl is a nuclear and cytoplasmic tyrosine kinase involved in a variety of cellular growth and differentiation processes. In contrast to its oncogenic counterparts, like BCR-Abl, c-Abl is not constitutively tyrosine phosphorylated and its catalytic activity is very low. Here we report tyrosine phosphorylation of endogenous c-Abl and a concomitant increase in catalytic activity. Using Abl -/- cells reconstituted with mutated c-Abl forms, we show that phosphorylation and activity depend on Tyr412 in the activation loop. Tyr412 is also required for stimulation by PDGF or by cotransfection of active Src. Phosphorylation of Tyr412 can occur autocatalytically by a trans-mechanism and cause activation of otherwise inactive c-Abl, suggesting a pos. feedback loop on c-Abl activity. In the recent structure of the Abl catalytic domain bound to the STI-571 inhibitor, unphosphorylated Tyr412 in the activation loop points inward and appears to interfere with catalysis. We mutated residues involved in stabilizing this inhibited form of the activation loop and in positioning Tyr412. These mutations resulted in tyrosine phosphorylation and activation of c-Abl, as if relieving c-Abl from inhibition. Tyr412 is therefore necessary both for activity and for regulation of c-Abl, by stabilizing the inactive or the active conformation of the enzyme in a phosphorylation-dependent manner.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 33 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:97935 CA
TITLE: Activated c-Abl is degraded by the ubiquitin-dependent proteasome pathway
AUTHOR(S): Echarri, Asier; Pendergast, Ann Marie
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: Current Biology (2001), 11(22), 1759-1765
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB C-Abl is a non-receptor tyrosine kinase that is tightly regulated in the cell. Genetic data derived from studies in flies and mice strongly support a role for Abl kinases in the regulation of the cytoskeleton. C-Abl can be activated by several stimuli, including oxidative stress, DNA damage, integrin engagement, growth factors, and Src family kinases. Structural alterations elicit constitutive activation of the c-Abl tyrosine kinase, leading to oncogenic transformation. While the mechanisms that activate c-Abl are beginning to be elucidated, little is known regarding the mechanisms that down-regulate activated c-Abl. Here, we show for the first time that activated c-Abl is down-regulated by the ubiquitin-dependent degradation pathway. Activated forms of c-Abl are more unstable than wild-type and kinase-inactive forms. Moreover, inhibition of the 26S proteasome leads to increased c-Abl levels in vitro and in cells, and activated c-Abl proteins are ubiquitinated in vivo. Significantly, inhibition of the 26S proteasome in fibroblasts increases the levels of tyrosine-phosphorylated, endogenous c-Abl. Our data suggest a novel mechanism for irreversible down-regulation of activated c-Abl, which is critical to prevent the deleterious consequences of c-Abl hyperactivation in mitogenic and cytoskeletal pathways.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 34 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:84625 CA
TITLE: Biological insights into TCRγδ+ and TCRαβ+ intraepithelial lymphocytes provided by serial analysis of gene expression (SAGE)
AUTHOR(S): Shires, John; Theodoridis, Efstathios; Hayday, Adrian C.
CORPORATE SOURCE: Peter Gorer Department of Immunobiology Guy's, King's, Medical School King's College, University of London, London, SE1 9RT, UK
SOURCE: Immunity (2001), 15(3), 419-434
CODEN: IUNIEH; ISSN: 1074-7613
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intraepithelial lymphocytes (IELs) are abundant, evolutionarily conserved T cells, commonly enriched in T cell receptor (TCR)γδ expression. However, their primary functional potential and constitutive activation state are incompletely understood. To address this, serial anal. of gene expression (SAGE) was applied to murine TCRγδ+ and TCRαβ+ intestinal IELs directly ex vivo, identifying 15,574 unique transcripts that collectively portray an "activated yet resting," Th1-skewed, cytolytic, and immunoregulatory phenotype applicable to multiple subsets of gut IELs. Expression of granzymes, Fas ligand, RANTES, prothymosin β4, junB, RGS1, Btg1, and related mols. is high, whereas expression of conventional cytokines and high-affinity cytokine receptors is low. Differentially expressed genes readily identify heterogeneity among TCRαβ+ IELs, whereas differences between resident TCRγδ+ IELs and TCRαβ+ IELs are less obvious.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 35 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:83711 CA
TITLE: Requirement for Mdm2 in the survival effects of Bcr-Abl and interleukin 3 in hematopoietic cells
AUTHOR(S): Goetz, Alexander W.; Van der Kuip, Heiko; Maya, Ruth; Oren, Moshe; Aulitzky, Walter E.
CORPORATE SOURCE: Dr. Margarete Fischer-Bosch Institute for Clinical Pharmacology, Stuttgart, Germany
SOURCE: Cancer Research (2001), 61(20), 7635-7641
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The p53/Mdm2 pathway plays an important role in the induction of cell cycle arrest or apoptosis in response to genotoxic stress. Both the oncogene Bcr-Abl and physiol. growth factors such as interleukin (IL)-3 can modulate the outcome of cellular exposure to DNA damage. To determine whether Bcr-Abl and growth factors can affect the p53/Mdm2 pathway, the authors studied the expression of Mdm2 in the IL-3-dependent pre-B cell line BaF3 and its bcr-abl-transfected derivative BaF3p185 after IL-3 deprivation or treatment with the c-Abl tyrosine kinase inhibitor STI 571. They found that both growth factor withdrawal and inhibition of Bcr-Abl kinase lead to a down-regulation of Mdm2 preceding the induction of apoptosis. Apoptotic cell death induced by STI 571 is partially dependent on p53. The early decrease of Mdm2 protein was not attributable to transcriptional regulation or to caspase-mediated cleavage. On the other hand, it could be completely blocked by the proteasomal inhibitor lactacystin. Targeted down-regulation of Mdm2 protein by antisense oligodeoxynucleotides overcame the survival effects of IL-3 and Bcr-Abl and resulted in accelerated apoptosis. Taken together, survival signals provided either by physiol. growth factors or by oncogenic Bcr-Abl can pos. regulate Mdm2, whereas Mdm2 ablation can reduce cell survival. Thus, similarly to physiol. growth factors such as IL-3, Bcr-Abl can promote cell survival via modulating the p53-Mdm2 pathway.
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 36 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:67452 CA
TITLE: Ceramide Blocks PDGF-Induced DNA Synthesis in Mesangial Cells via Inhibition of Akt Kinase in the Absence of Apoptosis
AUTHOR(S): Ghosh Choudhury, Goutam; Zhang, Jian-Hua; Ghosh-Choudhury, Nandini; Abboud, Hanna E.
CORPORATE SOURCE: Geriatric Research, Education and Clinical Center, San Antonio, TX, USA
SOURCE: Biochemical and Biophysical Research Communications ( 2001), 286(5), 1183-1190
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanism of action of ceramide in glomerular mesangial cells has not been studied. We investigated the effect of C2 ceramide on the mitogenic signal transduction pathways induced by PDGF in mesangial cells. Increasing concns. of C2 ceramide inhibited PDGF-induced DNA synthesis in a dose-dependent manner with maximum inhibition at 15 μM. This inhibition of DNA synthesis was associated with attenuation of PDGF-induced early response gene c-fos transcription. PDGF receptor β immunocomplex kinase assay showed no inhibitory effect of C2 ceramide on PDGF receptor tyrosine kinase activity. We have recently shown that the mitogenic effect of PDGF is mediated by the enzyme phosphatidylinositol (PI) 3 kinase in mesangial cells. C2 ceramide had no effect on PDGF-induced PDGFR-associated PI 3 kinase activity. These data indicate that inhibitory effect of C2 on PDGF-induced DNA synthesis is likely due to post-receptor and post-PI 3 kinase events. To address the mechanism of C2-mediated inhibition of DNA synthesis, we investigated the downstream target of PI 3 kinase, Akt. PDGF time-dependently increased Akt kinase activity in a PI 3 kinase-dependent manner. Incubation of mesangial cells with C2 ceramide inhibited PDGF-induced Akt activity. Akt kinase inhibits apoptosis of cells via phosphorylation of multiple proapoptotic proteins. However, inhibition of Akt activity by C2 ceramide did not induce apoptosis in mesangial cells. These data provide the first evidence that in mesangial cells, ceramide cross-talks with PI 3 kinase-dependent Akt kinase to inhibit PDGF-induced DNA synthesis without inducing apoptosis. (c) 2001 Academic Press.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 37 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:51990 CA
TITLE: Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease
AUTHOR(S): MacDonald, Tobey J.; Brown, Kevin M.; LaFleur, Bonnie; Peterson, Katia; Lawlor, Christopher; Chen, Yidong; Packer, Roger J.; Cogen, Philip; Stephan, Dietrich A.
CORPORATE SOURCE: Center for Cancer and Transplantation Biology, Children's National Medical Center, Washington, DC, USA
SOURCE: Nature Genetics (2001), 29(2), 143-152
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Little is known about the genetic regulation of medulloblastoma dissemination, but metastatic medulloblastoma is highly associated with poor outcome. We obtained expression profiles of 23 primary medulloblastomas clin. designated as either metastatic (M+) or non-metastatic (M0) and identified 85 genes whose expression differed significantly between classes. Using a class prediction algorithm based on these genes and a leave-one-out approach, we assigned sample class to these tumors (M+ or M0) with 72% accuracy and to four addnl. independent tumors with 100% accuracy. We also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably, platelet-derived growth factor receptor α ( PDGFRA) and members of the downstream RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway are upregulated in M+ tumors. Immunohistochem. validation on an independent set of tumors shows significant overexpression of PDGFRA in M+ tumors compared to M0 tumors. Using in vitro assays, we show that platelet-derived growth factor α (PDGFA) enhances medulloblastoma migration and increases downstream MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK) and MAPK3 (p44 MAPK) phosphorylation in a dose-dependent manner. Neutralizing antibodies to PDGFRA blocks MAP2K1, MAP2K2 and MAPK1/3 phosphorylation, whereas U0126, a highly specific inhibitor of MAP2K1 and MAP2K2, also blocks MAPK1/3. Both inhibit migration and prevent PDGFA-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for PDGFRA and the RAS/MAPK signaling pathway in medulloblastoma metastasis. Inhibitors of PDGFRA and RAS proteins should therefore be considered for investigation as possible novel therapeutic strategies against medulloblastoma.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 38 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:48663 CA
TITLE: Differential regulation of endochondral bone growth and joint development by FGFR1 and FGFR3 tyrosine kinase domains
AUTHOR(S): Wang, Qing; Green, Rebecca P.; Zhao, Guoyan; Ornitz, David M.
CORPORATE SOURCE: Department of Molecular Biology and Pharmacology, Washington University Medical School, St Louis, MO, 63110, USA
SOURCE: Development (Cambridge, United Kingdom) (2001 ), 128(19), 3867-3876
CODEN: DEVPED; ISSN: 0950-1991
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fibroblast growth factor receptors (FGFR) 1 and 3 have distinct mitogenic activities in vitro. In several cultured cell lines, FGFR1 transmits a potent mitogenic signal, whereas FGFR3 has little or no mitogenic activity. However, in other in vitro assays the FGFR3 intracellular domain is comparable with that of FGFR1. In vivo, FGFR3 neg. regulates chondrocyte proliferation and differentiation, and activating mutations are the mol. etiol. of achondroplasia. By contrast, FGFR1 transmits a proliferative signal in various cell types in vivo. These observations suggest that inhibition of the proliferating chondrocyte could be a unique property of FGFR3 or, alternatively, a unique property of the proliferating chondrocyte. To test this hypothesis, FGFR1 signaling was activated in the growth plate in cells that normally express FGFR3 ... Comparison of transgenic mice with an activated FGFR1 signaling pathway with an achondroplasia-like mouse that expresses a similarly activated FGFR3 signaling pathway demonstrated that both transgenes result in a similar achondroplasia-like dwarfism. These data demonstrate that suppression of mitogenic activity by FGFR signaling is a property that is unique to growth plate chondrocytes. Surprisingly, the authors observed that in transgenic mice expressing an activated FGFR, some synovial joints failed to develop and were replaced by cartilage. The defects in the digit joints phenocopied the symphalangism that occurs in Apert syndrome and the number of affected joints was dependent on transgene dose. In contrast to the phenotype in the growth plate, the joint phenotype was more severe in transgenic mice with an activated FGFR1 signaling pathway. The failure of joint development resulted from expanded chondrification in the presumptive joint space, suggesting a crucial role for FGF signaling in regulating the transition of condensed mesenchyme to cartilage and in defining the boundary of skeletal elements.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 39 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:48201 CA
TITLE: Efficacy of the novel selective platelet-derived growth factor receptor antagonist CT52923 on cellular proliferation, migration, and suppression of neointima following vascular injury
AUTHOR(S): Yu, Jin-Chen; Lokker, Nathalie A.; Hollenbach, Stanley; Apatira, Mutiah; Li, Jason; Betz, Andreas; Sedlock, David; Oda, Shoji; Nomoto, Yuji; Matsuno, Kenji; Ide, Shin-Ichi; Tsukuda, Eiji; Giese, Neill A.
CORPORATE SOURCE: COR Therapeutics, Inc., South San Francisco, CA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 298(3), 1172-1178
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exaggerated or inappropriate signaling by the platelet-derived growth factor receptor (PDGFR) tyrosine kinase has been implicated in a wide variety of diseases. Thus, a series of piperazinyl quinazoline compds. were identified as potent antagonists of the PDGFR by screening chemical libraries. An optimized analog, CT52923, was shown to be an ATP-competitive inhibitor that exhibited remarkable specificity when tested against other kinases, including all members of the closely related PDGFR family. The PDGFRs and stem cell factor receptor were inhibited with an IC50 of 100 to 200 nM, while 45- to >200-fold higher concns. of CT52923 were required to inhibit fms-like tyrosine kinase-3 and colony-stimulating factor-1 receptor, resp. Other receptor tyrosine kinases, cytoplasmic tyrosine kinases, serine/threonine kinases, or members of the mitogen-activated protein kinase pathway were not significantly inhibited at 100- to 1000-fold higher concns. In addition, this compound also demonstrated specificity for inhibition of cellular responses. Platelet-derived growth factor-induced smooth muscle cell migration or fibroblast proliferation was blocked by CT52923 with an IC50 of 64 and 280 nM, resp., whereas 50- to 100-fold higher concns. were required to inhibit these responses when induced with fibroblast growth factor. To investigate the effect of CT52923 on PDGFR signaling, in vivo studies demonstrated that CT52923 could significantly inhibit neointima formation following carotid artery injury by oral administration in the rat. Therefore, PDGFR antagonism by CT52923 could be a viable strategy for the prevention of clin. restenosis or the treatment of other human diseases involving PDGFR signaling.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 40 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:32265 CA
TITLE: Competitive polymerase chain reaction as a method to detect the amplification of bcr-abl gene of chronic myeloid leukemia
AUTHOR(S): Campanini, Fabio; Santucci, Maria Alessandra; Pattacini, Laura; Bruss, Gianluca; Piccioli, Milena; Barbieri, Enza; Babini, Lucio; Tura, Sante
CORPORATE SOURCE: Istituto di Ematologia e Oncologia Medica "L.A. Seragnoli", University of Bologna Medical School, Bologna, Italy
SOURCE: Haematologica (2001), 86(2), 167-173
CODEN: HAEMAX; ISSN: 0390-6078
PUBLISHER: Ferrata Storti Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The chimeric product of the bcr-abl rearranged gene is critical in the pathogenesis of chronic myeloid leukemia (CML), yet its role in the progression of the disease remains unclear. There is some evidence that increased bcr-abl expression levels, possibly due to gene amplification, precede the clonal evolution of CML hematopoietic progenitors toward a fully transformed phenotype and might be involved in their resistance to interferon-alpha or tyrosine kinase inhibitors . To quantify the bcr-abl gene both at the genomic and at the transcriptional levels we developed a competitive polymerase chain reaction (PCR) strategy. The competitive PCR technique is based upon the co-amplification of the sample template (target) together with increasing amts. of a DNA fragment (competitor) sharing with the target the primer recognition sites, but differing in size. We constructed a competitor for the quantification of both b2a2 and b3a2 alternative splicing forms of the bcr-abl chimera and established the accuracy and reproducibility of our competitive strategy in a clone of the murine 32DG hematopoietic cell line (32D LG7), which bears a stable integration of a single copy of p210 bcr-abl fusion gene. We utilized this technique to follow, over a period of 200 days, the fusion gene copy nos. and transcription rates in several p210 bcr-abl-transduced 32D cell clones, an exptl. condition mimicking the evolution of CML myeloid progenitors in vivo. Our results are consistent with p210 bcr-abl over-expression but not gene amplification associated with their clonal evolution. Increased p210 bcr-abl transcription rate is associated with the abrogation of radiation-induced apoptotic cell death, suggesting a role for the chimeric gene expression level in cell life expectancy after a genotoxic insult. We conclude that the assessment of gene amplification and expression might serve to improve prognostic classification and follow-up of CML patients.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 41 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:15030 CA
TITLE: STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications
AUTHOR(S): Tuveson, David A.; Willis, Nicholas A.; Jacks, Tyler; Griffin, James D.; Singer, Samuel; Fletcher, Christopher D. M.; Fletcher, Jonathan A.; Demetri, George D.
CORPORATE SOURCE: MIT Cancer Center and Department of Biology, Cambridge, MA, 02139, USA
SOURCE: Oncogene (2001), 20(36), 5054-5058
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mutations in the c-KIT receptor occur somatically in many sporadic Gastrointestinal Stromal Tumors (GIST), and similar mutations have been identified at the germline level in kindreds with multiple GISTs. These mutations activate the tyrosine kinase activity of c-KIT and induce constitutive signaling. To investigate the function of activated c-KIT in GIST, we established a human GIST cell line, GIST882, which expresses an activating KIT mutation (K642E) in the first part of the cytoplasmic split tyrosine kinase domain. Notably, the K642E substitution is encoded by a homozygous exon 13 missense mutation, and, therefore, GIST882 cells do not express native KIT. GIST882 c-KIT protein is constitutively tyrosine phosphorylated, but tyrosine phosphorylation was rapidly and completely abolished after incubating the cells with the selective tyrosine kinase inhibitor STI571. Furthermore, GIST882 cells evidenced decreased proliferation and the onset of apoptotic cell death after prolonged incubation with STI571. Similar results were obtained after administering STI571 to a primary GIST cell culture that expressed a c-KIT exon 11 juxtamembrane mutation (K558NP). These cell-culture-based studies support an important role for c-KIT signaling in GIST and suggest therapeutic potential for STI571 in patients afflicted by this chemoresistant tumor.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 42 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:3858 CA
TITLE: Phosphatidylinositol 3 kinase contributes to the transformation of hematopoietic cells by the D816V c-Kit mutant
AUTHOR(S): Chian, RuJu; Young, Sonia; Danilkovitch-Miagkova, Alla; Ronnstrand, Lars; Leonard, Edward; Ferrao, Petranel; Ashman, Leonie; Linnekin, Diana
CORPORATE SOURCE: Basic Research Laboratory and the Laboratory of Immunobiology, Division of Basic Sciences, National Cancer Institute-Frederick, Frederick, MD, 21702, USA
SOURCE: Blood (2001), 98(5), 1365-1373
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Stem cell factor (SCF) binds the receptor tyrosine kinase c-Kit and is critical for normal hematopoiesis. Substitution of valine for aspartic acid 816 (D816V) constitutively actives human c-Kit, and this mutation is found in patients with mastocytosis, leukemia, and germ cell tumors. Immortalized murine progenitor cells (MIHCs) transduced with wild-type c-Kit proliferate in response to SCF, whereas cells expressing D816V c-Kit (MIHC-D816V) are factor-independent and tumorigenic. However, the mechanisms mediating transformation by D816V c-Kit are unknown. The objective of this study was to identify signaling components that contribute to D816V c-Kit-mediated transformation. SCF stimulates association of p85PI3K with phosphorylated tyrosine 721 of wild-type c-Kit. Phosphatidylinositol 3 kinase (PI3K) subsequently contributes to the activation of Akt and Jnks. In contrast, these studies demonstrated that the D816V c-Kit mutant was constitutively associated with phosphorylated p85PI3K, and, downstream of PI3K, Jnk 1 and Jnk 2 were activated but Akt was not. Interestingly, Erks 1 and 2 were not constitutively activated by D816V c-Kit . Thus, D816V c-Kit maintains the activity of PI3K but not of all signaling pathways activated by wild-type c-Kit. Further, all pathways downstream of PI3K are not constitutively active in MIHC-D816V cells. Studies with a PI3K inhibitor and D816V/Y721F c-Kit, a mutant incapable of recruiting PI3K, indicate that constitutive activation of PI3K through direct recruitment by D816V c-Kit plays a role in factor-independent growth of MIHC and is critical for tumorigenicity.
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 43 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 135:369808 CA
TITLE: Mechanisms of transformation by the BCR/ABL oncogene
AUTHOR(S): Sattler, Martin; Griffin, James D.
CORPORATE SOURCE: Department of Adult Oncology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
SOURCE: International Journal of Hematology (2001), 73(3), 278-291
CODEN: IJHEEY; ISSN: 0925-5710
PUBLISHER: Carden Jennings Publishing
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with refs. The Philadelphia chromosome generates a chimeric oncogene in which the BCR and c-ABL genes are fused. The product of this oncogene, BCR/ABL, has elevated ABL tyrosine kinase activity, relocates to the cytoskeleton, and phosphorylates multiple cellular substrates. BCR/ABL transforms hematopoietic cells and exerts a wide variety of biol. effects, including reduction in growth factor dependence, enhanced viability, and altered adhesion of chronic myelocytic leukemia (CML) cells. Elevated tyrosine kinase activity of BCR/ABL is critical for activating downstream signal transduction and for all aspects of transformation. This review will describe mechanisms of transformation by the BCR/ABL oncogene and opportunities for clin. intervention with specific signal transduction inhibitors such as STI-571 in CML.
REFERENCE COUNT: 212 THERE ARE 212 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 44 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 135:357926 CA
TITLE: Synthesis of indolinone vinyl-derivatives used to modulate protein kinase activity
INVENTOR(S): Tang, Peng Cho; Sun, Li; Mcmahon, Gerald; Harris, G. David
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: U.S., 29 pp., Cont.-in-part of U.S. Ser. No. 212,494.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6316635 | B1 | 20011113 | US 1999-293518 | 19990415 |
| US 5880141 | A | 19990309 | US 1995-485323 | 19950607 |
| US 5792783 | A | 19980811 | US 1996-655223 | 19960605 |
| US 5883113 | A | 19990316 | US 1996-659191 | 19960605 |
| EP 934931 | A2 | 19990811 | EP 1999-103667 | 19960605 |
| EP 934931 | A3 | 19991020 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI | | | | |
| JP 2000026412 | A2 | 20000125 | JP 1999-159567 | 19960605 |
| US 6225335 | B1 | 20010501 | US 1998-212494 | 19981215 |
| US 2001027207 | A1 | 20011004 | US 2001-765619 | 20010122 |
| US 6469032 | B2 | 20021022 | | |
| US 2002028840 | A1 | 20020307 | US 2001-899550 | 20010706 |
| US 6569868 | B2 | 20030527 | | |
| US 2003191128 | A1 | 20031009 | US 2003-372341 | 20030225 |
| PRIORITY APPLN. INFO.: | | | US 1995-485323 | A2 19950607 |
| | | | US 1996-655223 | A2 19960605 |
| | | | US 1996-659191 | A1 19960605 |
| | | | US 1998-82056P | P 19980416 |
| | | | US 1998-212494 | A2 19981215 |
| | | | EP 1996-918093 | A3 19960605 |
| | | | JP 1997-501363 | A3 19960605 |
| | | | US 1999-293518 | A1 19990415 |
| | | | US 2001-899550 | A3 20010706 |

L13 ANSWER 44 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)
OTHER SOURCE(S): MARPAT 135:357926
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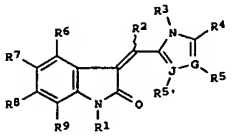

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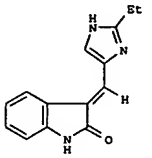

II

AB Title compds. I [G, J = N such that, when G = N, J = C and when J = N, G = C, it being recognized that, when G or J = N, R5 or R5' does not exist; R1-3 = H; R4, R5, R5' H, alk(en/yn)yl, cycloalkyl, aryl, heteroaryl, heteroalicylic, halo, hydroxy, nitro, cyano, alkoxy, aryloxy, etc.; R6-9 = H, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, etc.] with some exceptions, were prepared For instance, 2-ethyl-4-formylimidazole was reacted with resin bound 2-chlorotriphenylmethyl chloride (CH2Cl2, iPr2NEt, 21 h, room temperature) and the isolated product condensed with 2-indolinone (DMF, piperidine, 80°C, 20 h) to give the corresponding resin-bound 2-indolinone. The resin bound intermediate was cleaved (CH2Cl2, TFA, 2 h, room temperature) to give II as the TFA salt of a 10:1 E/Z mixture I exhibit kinase inhibitory activity and are useful for treating, e.g., diabetes, autoimmune disorder, etc.
REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 44 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)

L13 ANSWER 45 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 135:356752 CA
TITLE: Epitope synchronization in antigen presenting cells
INVENTOR(S): Simard, John J. L.; Diamond, David C.; Lei, Xiang-Dong
PATENT ASSIGNEE(S): CTL Immunotherapies Corp., USA
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001082963 | A2 | 20011108 | WO 2001-US13806 | 20010427 |
| WO 2001082963 | A3 | 20020411 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6861234 | B1 | 20050301 | US 2000-561074 | 20000428 |
| CA 2405363 | AA | 20011108 | CA 2001-2405363 | 20010427 |
| EP 1276896 | A2 | 20030122 | EP 2001-930922 | 20010427 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003535824 | T2 | 20031202 | JP 2001-579836 | 20010427 |
| US 2005130920 | A1 | 20050616 | US 2004-895523 | 20040720 |
| US 2005069982 | A1 | 20050331 | US 2004-956401 | 20041001 |
| PRIORITY APPLN. INFO.: | | | US 2000-560465 | A 20000428 |
| | | | US 2000-561074 | A 20000428 |
| | | | US 2000-561571 | A 20000428 |
| | | | US 2000-561572 | A 20000428 |
| | | | WO 2001-US13806 | W 20010427 |
| | | | US 2001-5905 | B1 20011107 |
| | | | US 2001-999186 | A1 20011107 |
| | | | US 2001-26066 | A1 20011207 |

AB Disclosed herein are vaccines and methods for inducing an immune response against cancer cells and cells infected with intracellular parasites. Vaccines having housekeeping epitopes are disclosed. The housekeeping epitope is formed by housekeeping proteasomes in peripheral cells, but not by professional antigen presenting cells. A vaccine containing a housekeeping epitope that is derived from an antigen associated with a peripheral target

L13 ANSWER 45 OF 475 CA COPYRIGHT 2006 ACS on STN (Continued)
cell can thus direct an immune response against the target cell. Methods of treatment are also disclosed, which involve administering a vaccine having a housekeeping epitope.

L13 ANSWER 46 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 135:352438 CA
TITLE: Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification
AUTHOR(S): Gorre, Mercedes E.; Mohammed, Mansoor; Ellwood, Katharine; Hsu, Nicholas; Paquette, Ron; Rao, P. Nagesh; Sawyers, Charles L.
CORPORATE SOURCE: Department of Medicine, University of California, Los Angeles, CA, 90095, USA
SOURCE: Science (Washington, DC, United States) (2001), 293(5531), 876-880
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Clin. studies with the Abl tyrosine kinase inhibitor STI-571 in chronic myeloid leukemia demonstrate that many patients with advanced stage disease respond initially but then relapse. Through biochem. and mol. anal. of clin. material, we find that drug resistance is associated with the reactivation of BCR-ABL signal transduction in all cases examined In six of nine patients, resistance was associated with a single amino acid substitution in a threonine residue of the Abl kinase domain known to form a critical hydrogen bond with the drug. This substitution of threonine with isoleucine was sufficient to confer STI-571 resistance in a reconstitution experiment In three patients, resistance was associated with progressive BCR-ABL gene amplification. These studies provide evidence that genetically complex cancers retain dependence on an initial oncogenic event and suggest STI-571 resistance.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 47 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 135:330346 CA
TITLE: CIS1, a cytokine-inducible SH2 protein, suppresses BCR/ABL-mediated transformation: Involvement of the ubiquitin proteasome pathway
AUTHOR(S): Tauchi, T.; Yoshimura, A.; Ohyashiki, K.
CORPORATE SOURCE: First Department of Internal Medicine, Tokyo Medical University, Tokyo, Japan
SOURCE: Experimental Hematology (New York, NY, United States) (2001), 29(3), 356-361
CODEN: EXHMA6; ISSN: 0301-472X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB BCR/ABL is a chimeric oncoprotein that exhibits deregulated tyrosine kinase activity and is implicated in the pathogenesis of Philadelphia chromosome (Ph)-pos. leukemia. A general understanding of BCR/ABL signaling events is emerging, but little is known about the endogenous inhibitors of p210 BCR/ABL. The present study focused attention on CIS1, a cytokine-inducible SH2 protein, as a potential physiol. antagonist for BCR/ABL.The murine hematopoietic cell line NSF/N1.H7 stably transfected with BCR/ABL was compared to the parental counterparts for induction of CIS1 by immunoblotting and immunopptn. Cells were treated with a proteasome inhibitor to examine the effect of a proteasome inhibitor on CIS1 protein expression. To determine the effect of CIS1 on BCR/ABL-mediated transformation, we generated Rat-1 fibroblasts transfected with either a control vector, CIS1, BCR/ABL p210, or CIS1 plus BCR/ABL p210.Three forms of CIS1 with mol. masses of 32, 37, and 47 kDa were detected in BCR/ABL-transformed cells. The 47-kDa protein was a ubiquitinated protein. The proteasome inhibitor increased the formation of complexes between CIS1 and BCR/ABL. Transformation of p210 BCR/ABL was significantly suppressed in cells overexpressing CIS1.The results suggest that CIS1 is an endogenous inhibitor of p210 BCR/ABL and is likely to be important in the pathogenesis of Ph-pos. leukemia.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 48 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 135:329589 CA
TITLE: Identification of a subpopulation of rapidly self-renewing and multipotential adult stem cells in colonies of human marrow stromal cells
AUTHOR(S): Colter, David C.; Sekiya, Ichiro; Prockop, Darwin J.
CORPORATE SOURCE: Center for Gene Therapy, Tulane University Health Sciences Center, New Orleans, LA, 70112, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(14), 7841-7845
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Marrow stromal cells are adult stem cells from bone marrow that can differentiate into multiple nonhematopoietic cell lineages. Previous reports demonstrated that single-cell-derived colonies of marrow stromal cells contained two morphol. distinct cell types: spindle-shaped cells and large flat cells. Here we found that early colonies also contain a third kind of cell: very small round cells that rapidly self-renew. Samples enriched for the small cells had a greater potential for multipotential differentiation than samples enriched for the large cells. Also, the small cells expressed a series of surface epitopes and other proteins that potentially can be used to distinguish the small cells from the large cells. The results suggested it will be important to distinguish the major subpopulations of marrow stromal cells in defining their biol. and their potential for cell and gene therapy.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 49 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 135:312950 CA
TITLE: STI571: Targeting BCR-ABL as therapy for CML
AUTHOR(S): Mauro, Michael J.; Druker, Brian J.
CORPORATE SOURCE: Leukemia Program, Division of Hematology and Medical Oncology, Oregon Health Sciences University, Portland, OR, 97201, USA
SOURCE: Oncologist (2001), 6(3), 233-238
CODEN: OCOLF6; ISSN: 1083-7159
PUBLISHER: AlphaMed Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with refs. Therapeutic agent STI571 (signal transduction inhibitor number 571) is a rationally developed, potent, and selective inhibitor for abl tyrosine kinases, including bcr-abl, as well c-kit and the platelet-derived growth factor receptor tyrosine kinases. Results of clin. trials to date have demonstrated the crucial role of the bcr-abl tyrosine kinase in chronic myelogenous leukemia (CML) pathogenesis and the potential of anticancer agents designed to target specific mol. abnormalities in human cancer. An initial phase I study of STI571 included 83 Ph+ CML patients who had failed interferon-based therapy. Patients were required to be in chronic phase, defined liberally as less than 15% blasts in blood or bone marrow. Patients were treated with once-daily oral doses of STI571 in 14 successive dose cohorts ranging from 25-1,000 mg. In this phase I study, no dose-limiting toxicity was encountered and toxicity at all dose levels was minimal. The threshold for a maximally ED was found at 300 mg; for patients treated at or above this level, complete hematol. response was seen in 98% of patients, with complete cytogenetic responses in 13% and major cytogenetic responses in 31%. With a median duration of follow-up of 310 days, ongoing responses are evident in 96% of patients. In the phase II study of the accelerated phase of CML, 233 patients were treated with either 400 or 600 mg of STI571. With similar follow-up to the chronic phase trial, 91% of patients showed a hematol. response; 63% of patients achieved a complete hematol. response but not all patients had recovery of peripheral blood counts. In addition to the phase II clin. trials with STI571, a phase III trial randomizing newly diagnosed patients to either interferon with low-dose s.c. cytosine arabinoside vs. STI571 is ongoing; this trial accrued rapidly and data collection is ongoing. Integration of STI571 into CML treatment algorithms will require long-term follow-up data from the ongoing phase II and III clin. studies.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 50 OF 475 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 135:302488 CA
TITLE: The Kit-activating mutation D816V enhances stem cell factor-dependent chemotaxis
AUTHOR(S): Taylor, Marcia L.; Dastych, Jaroslaw; Sehgal, Devinder; Sundstrom, Magnus; Nilsson, Gunnar; Akin, Cem; Mage, Rose G.; Metcalfe, Dean D.
CORPORATE SOURCE: Laboratory of Allergic Diseases and Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, 20892-1881, USA
SOURCE: Blood (2001), 98(4), 1195-1199
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The D816V mutation of c-kit has been detected in patients with mastocytosis. This mutation leads to constitutive tyrosine kinase activation of Kit. Because stem cell factor (SCF), the ligand for Kit (CD117+), is a chemoattractant for CD117+ cells and one feature of mastocytosis is an abnormal collection of mast cells in tissues derived from CD34+CD117+ mast cell precursors, the hypothesis was considered that the D816V mutation would enhance chemotaxis of these precursor cells. Constructs encoding wild-type Kit or Kit bearing the D816V mutation were transfected into Jurkat cells, labeled with Calcein-AM, and migration to SCF assessed in the presence or absence of tyrosine kinase inhibitors. Chemotaxis to SCF was enhanced in D816V transfectants compared to wild-type Kit transfectants. Migration of both transfectants was inhibited by tyrosine kinase inhibitors, although D816V transfectants were more sensitive. Chemotaxis was next performed on CD34+CD117+ circulating mast cell precursors obtained from patients with mastocytosis. Anal. of prechemotaxia and migrated cells showed that whereas less than 10% in the prechemotaxis sample had the D816V mutation, 40% to 80% of migrated cells had this mutation. These results demonstrate that the D816V Kit mutation enhances chemotaxis of CD117+ cells, offering one explanation for increased mast cells observed in tissues of patients with mastocytosis.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d his

     (FILE 'HOME' ENTERED AT 09:57:19 ON 14 SEP 2006)

     FILE 'REGISTRY' ENTERED AT 09:57:31 ON 14 SEP 2006
L1              STRUCTURE UPLOADED
L2           50 S L1 SAM
L3         1572 S L1 FULL

     FILE 'CA' ENTERED AT 09:59:02 ON 14 SEP 2006
L4           19 S L3
L5        36780 S TYROSINE KINASE
L6           12 S L4 AND L5
L7            7 S L4 NOT L6
L8         6194 S C-KIT OR C-ABL OR BEGFR3
L9         2585 S PDGFR? OR FGFR3 OR FLT-3 OR P60SRC
L10        8481 S L8 OR L9
L11        2606 S L10 AND L5
L12        1302 S L11 AND INHIB?
L13         475 S L12 AND PY<2002

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y
 INTERNATIONAL LOGOFF AT 10:02:23 ON 14 SEP 2006
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